Poster 432P

Exploratory biomarker analysis of trastuzumab deruxtecan versus treatment of physician's choice in HER2-low, hormone receptor–positive metastatic breast cancer in DESTINY-Breast04

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Objective

- As part of the exploratory objectives of DESTINY-Breast04 (NCT03734029), relationships of baseline biomarkers for human epidermal growth factor receptor 2 (HER2) expression and mutation, DNA damage response (DDR) or cell proliferation, *BRCA1/2* or homologous recombination repair (HRR) gene alteration, and the tumor microenvironment with clinical outcomes were explored in patients with HER2-low, hormone receptor–positive (HR+) metastatic breast cancer (mBC) treated with trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC)

Conclusions

- Treatment with T-DXd demonstrated clinically meaningful improvement in progression-free survival (PFS) and confirmed objective response rate (cORR) compared with TPC across biomarker-defined subgroups, including *HER2* gene expression or mutation, *BRCA1/2* or HRR gene alteration status, DDR/cell proliferation gene expression signature status, and tumor microenvironment status
- Based on these results, there does not appear to be a singular mechanism of sensitivity or resistance to T-DXd compared with TPC in DESTINY-Breast04, which is consistent with another study[1]
- Limitations of this analysis include the low patient numbers in some biomarker subgroups and limitations of circulating tumor DNA panel sequencing for detection of structural variants (*BRCA1/2* and HRR alteration status)

Plain language summary

Why did we perform this research?
Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate that can direct its chemotherapy payload specifically to tumor cells that express a protein called human epidermal growth factor receptor 2 (HER2) and affect neighboring cells that may not express HER2.[1] Breast cancer can be categorized by measuring the amount of HER2 protein expressed on the surface of tumor cells. In DESTINY-Breast04, a clinical trial in patients with metastatic breast cancer (mBC) whose tumors express low levels of HER2, T-DXd resulted in better treatment outcomes versus chemotherapy of physician's choice (TPC),[2] which led to the approval of T-DXd for the treatment of patients with HER2-low metastatic breast cancer.[3,4] The benefit of T-DXd over TPC in patients with HER2-low mBC in DESTINY-Breast04 has been shown regardless of the level of HER2 protein expression, the molecular subtype of the tumor, the presence or absence of certain tumor mutations, or markers of resistance to other therapies.[5] In the current analysis, we investigated the effect of T-DXd according to *HER2* gene expression or mutation, biomarkers of DNA damage or cell proliferation to assess the effect of the topoisomerase I chemotherapy agent of T-DXd, and biomarkers of tumor microenvironment immune status.

How did we perform this research?
Blood or tumor tissue samples collected from patients in DESTINY-Breast04 before they started the trial treatment (T-DXd or TPC) were measured to determine the levels of biomarkers, gene expression, or gene alterations. Biomarkers were categorized as having high or low levels based on the median value or as the presence or absence of a specific gene alteration. Clinical outcomes were assessed to investigate whether biomarker levels or gene alterations were associated with the effect of treatment with T-DXd versus TPC.

What were the findings of this research?
Treatment with T-DXd consistently demonstrated clinically meaningful improvement in outcomes compared with TPC across all the biomarker groups analyzed, including *HER2* gene expression or mutation, DNA damage and cell proliferation biomarkers, and tumor microenvironment immune status.

What were the implications of this research?
These results demonstrated that the clinical outcomes of T-DXd do not appear to be influenced by the biomarkers assessed in this analysis.

Where can I access more information?
DESTINY-Breast04: ClinicalTrial.gov. Trastuzumab Deruxtecan (DS-8201a) Versus Investigator's Choice for HER2-Low Breast Cancer That Has Spread or Cannot Be Surgically Removed. https://www.clinicaltrials.gov/ct2/show/NCT03734029

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Introduction

- T-DXd is a HER2-directed antibody-drug conjugate that can target tumor cells with low levels of HER2 expression and deliver the DXd payload to neighboring tumor cells, regardless of HER2 protein expression, through the bystander antitumor effect[2,3]
- Based on results of the DESTINY-Breast04 trial, T-DXd is approved for the treatment of patients with unresectable or metastatic HER2-low (immunohistochemistry [IHC] score 1+ or IHC 2+ and in situ hybridization–negative [ISH-]) breast cancer who have received chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy[4,5]
- DESTINY-Breast04 demonstrated significantly longer PFS and overall survival for T-DXd versus TPC, and clinical benefit was observed regardless of HER2 IHC status or previous treatment with cyclin-dependent kinase 4/6 inhibitors[6]
- Previous exploratory biomarker analysis in DESTINY-Breast04 demonstrated that the clinical benefit of T-DXd versus TPC was observed regardless of intrinsic subtype (HER2-enriched, luminal A, or luminal B), *ESR1* or *PIK3CA* gene mutation status, or the presence or absence of known markers of cyclin-dependent kinase 4/6 inhibitor resistance[7]
- The cytotoxic payload of T-DXd is a topoisomerase I inhibitor[8]; therefore, biomarkers of DDR and cell proliferation pathways were hypothesized to be potentially predictive or prognostic of response.[9] Preclinical research suggests that T-DXd increases antitumoral immune cells in the tumor microenvironment[5]; therefore, biomarkers of the tumor microenvironment immune status, such as total lymphocyte levels, were hypothesized to be associated with antitumor activity[10]

Methods

- We performed this exploratory biomarker analysis in patients with HER2-low HR+ mBC enrolled in DESTINY-Breast04 (data cutoff, January 11, 2022)
- Samples for biomarker analysis were collected at baseline before study treatment, after the last line of prior systemic therapy
  - Gene expression levels were derived from RNA sequencing, performed on tumor tissue samples. Gene expression signature scores were calculated using the single sample gene set enrichment analysis method[11] with the Molecular Signature Database hallmark gene set[12]
  - Circulating tumor DNA (ctDNA) plasma samples were analyzed using the Guardant OMNI panel (approximately 500 genes) to detect *HER2*-activating mutations (defined as *HER2* gain of function mutation according to the OncoKB database), *BRCA1/2* inactivating alterations (nonsense mutations, frameshift insertions/deletions, splice site alterations, homozygous deletions, loss of heterozygosity deletions), per the Guardant pipeline, and HRR gene alterations (per published methods[13])
  - Multicolor IHC analysis was performed on baseline (pretreatment) tumor tissue samples to determine the density of immune cells. Levels of total lymphocytes (including T cells, B cells, and natural killer [NK] cells), M1 macrophages, CD8+ T cells, CD56+ NK cells, CD4+ T cells, CD20+ B cells, and CD8+Ki67+ T cells were defined as immune active tumor microenvironment markers and levels of regulatory T cells (Tregs), PD1+ T cells, and M2 macrophages were defined as immune suppressive tumor microenvironment markers
- High versus low biomarker levels were defined, respectively, as greater than or equal to versus lower than the median value across the entire biomarker dataset
- We investigated relationships between biomarker status and clinical outcomes of cORR or PFS. Median PFS (mPFS) was estimated using the Kaplan-Meier method, and hazard ratios were calculated by comparing T-DXd with TPC. *P* values for biomarker interaction were assessed for T-DXd. The threshold for significance was *P* <0.05

Results

- Overall, cORR was higher and mPFS was longer with T-DXd versus TPC in the biomarker-defined populations, which was consistent with the intention-to-treat (ITT) population, and clinical outcomes were comparable between the biomarker-evaluable populations (**QR code Supplementary Table 1**)

HER2 status

- The clinical benefit of T-DXd over TPC was observed regardless of HER2 IHC status, *HER2* gene expression level, or *HER2* mutation status, and there was no statistically significant interaction based on these HER2 biomarkers (**Figures 1, 2, QR code Supplementary Figure 1**)
  - A non–significant trend for improved cORR (**Figure 1A**) and longer PFS (**Figure 2B**) was apparent in patients with higher versus lower *HER2* gene expression levels, particularly in the T-DXd arm

DDR and cell proliferation signatures

- The clinical benefit of T-DXd over TPC was observed regardless of the level of DDR or cell proliferation gene expression signatures, and there was no statistically significant biomarker interaction (**Figure 3, QR code Supplementary Figure 2**)
  - cORR was similar between patients with high and low levels of DDR or cell proliferation gene expression signatures (**QR code Supplementary Figure 2A**). Although the interaction *P* value was <0.05 for the G2/M checkpoint gene expression signature, the range of signatures examined, representing cell proliferation and DDR transcriptional programs, did not show any significant association. Overall, a consistent, but non–statistically significant, trend for shorter PFS in both treatment arms was observed in patients with higher levels of DDR or cell proliferation gene expression signatures (**QR code Supplementary Figure 2B**)

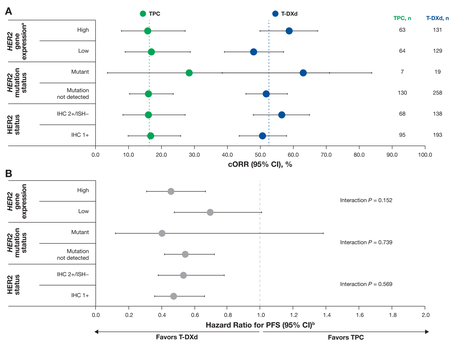
BRCA1/2 and HRR alteration status

- The clinical benefit of T-DXd over TPC was maintained regardless of *BRCA1/2* or HRR gene alteration status, and there was no statistically significant biomarker interaction (**Figure 4, Supplementary Figure 3A**)
  - A trend for shorter PFS was observed in both treatment arms for patients with *BRCA1/2* or HRR gene alterations compared with those with no alterations detected

Tumor microenvironment status

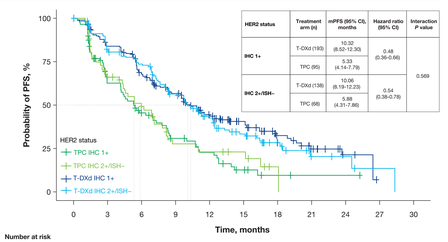
- The clinical benefit of T-DXd over TPC was observed for the majority of immune features measured by multicolor IHC analysis (**Figures 5, 6**)
  - For patients with higher levels of total lymphocytes in the stroma, a trend towards longer PFS was observed compared with those with lower levels in both treatment arms (**Figure 6**), which was consistent with trends observed across immune active subgroups (**Figure 5B**)
  - A consistent trend towards longer PFS was observed with a majority of tumoral and stromal immune markers (**Figure 5**)

Figure 1. Association of baseline HER2-related biomarkers with (A) cORR and (B) hazard ratio for PFS

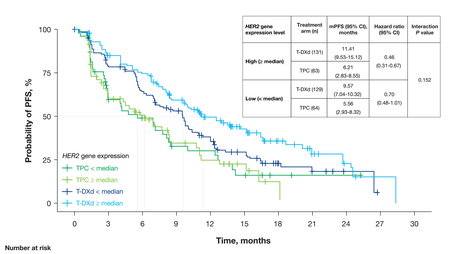


Dashed vertical lines in panel A show cORR in the HR+ ITT population.
[a]High and low were defined according to the median value.
[b]Hazard ratio for T-DXd vs TPC.

Figure 2. Probability of PFS according to (A) HER2 IHC status and (B) *HER2* gene expression at baseline



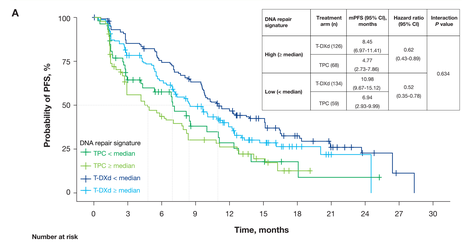
HER2 status	Treatment arm (n)	mPFS (95% CI), months	Hazard ratio (95% CI)	Interaction *P* value
IHC 1+	T-DXd (193)	10.32 (8.02-12.32)	0.48 (0.36-0.66)	0.569
	TPC (95)	5.33 (4.14-7.79)		
IHC 2+/ISH−	T-DXd (138)	10.06 (8.19-12.23)	0.54 (0.38-0.78)	
	TPC (68)	5.86 (4.31-7.86)		



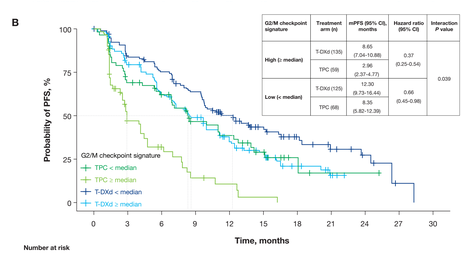
HER2 gene expression level	Treatment arm (n)	mPFS (95% CI), months	Hazard ratio (95% CI)	Interaction *P* value
High (≥ median)	T-DXd (131)	11.41 (9.53-15.12)	0.46 (0.31-0.67)	0.152
	TPC (63)	6.21 (2.83-8.55)		
Low (< median)	T-DXd (129)	9.57 (7.04-10.32)	0.70 (0.48-1.01)	
	TPC (64)	5.56 (2.93-8.32)		

Median PFS was estimated by the Kaplan-Meier method, and the hazard ratio was calculated comparing the T-DXd and TPC arms in each biomarker-derived subgroup.

Figure 3. Probability of PFS according to (A) DNA repair and (B) G2/M checkpoint gene expression signature levels at baseline



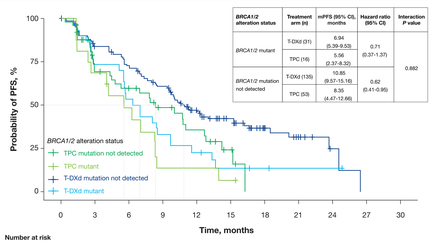
DNA repair signature	Treatment arm (n)	mPFS (95% CI), months	Hazard ratio (95% CI)	Interaction *P* value
High (≥ median)	T-DXd (126)	8.45 (6.97-11.41)	0.62 (0.43-0.89)	0.634
	TPC (68)	4.77 (2.73-7.86)		
Low (< median)	T-DXd (134)	10.98 (8.67-15.12)	0.52 (0.35-0.78)	
	TPC (59)	6.94 (2.93-9.99)		



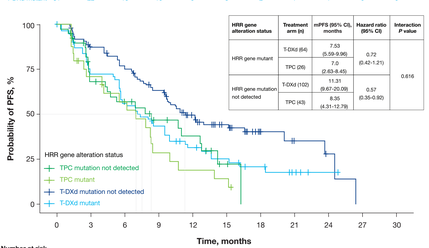
G2/M checkpoint signature	Treatment arm (n)	mPFS (95% CI), months	Hazard ratio (95% CI)	Interaction *P* value
High (≥ median)	T-DXd (135)	8.65 (7.04-10.88)	0.37 (0.25-0.54)	0.039
	TPC (59)	2.96 (2.37-4.77)		
Low (< median)	T-DXd (125)	12.30 (9.73-16.44)	0.66 (0.45-0.98)	
	TPC (68)	8.35 (5.82-12.39)		

Median PFS was estimated by the Kaplan-Meier method, and the hazard ratio was calculated comparing the T-DXd and TPC arms in each biomarker-derived subgroup.

Figure 4. Probability of PFS according to (A) *BRCA1/2* and (B) HRR gene alteration status at baseline



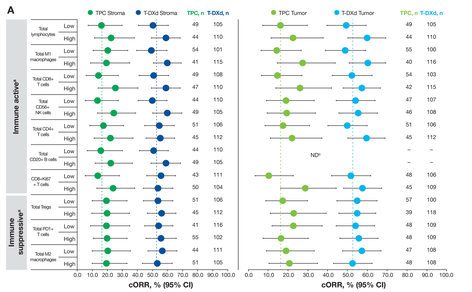
BRCA1/2 alteration status	Treatment arm (n)	mPFS (95% CI), months	Hazard ratio (95% CI)	Interaction *P* value
BRCA1/2 mutant	T-DXd (31)	6.94 (5.39-9.53)	0.71 (0.37-1.37)	0.882
	TPC (16)	5.56 (2.37-8.32)		
BRCA1/2 mutation not detected	T-DXd (135)	10.85 (9.57-15.16)	0.62 (0.47-0.85)	
	TPC (53)	8.35 (4.47-12.66)		



HRR gene alteration status	Treatment arm (n)	mPFS (95% CI), months	Hazard ratio (95% CI)	Interaction *P* value
HRR gene mutant	T-DXd (64)	7.53 (5.59-9.96)	0.72 (0.42-1.21)	0.616
	TPC (26)	2.96 (2.63-6.45)		
HRR gene mutation not detected	T-DXd (102)	11.31 (9.67-20.09)	0.57 (0.35-0.92)	
	TPC (43)	8.35 (4.31-12.79)		

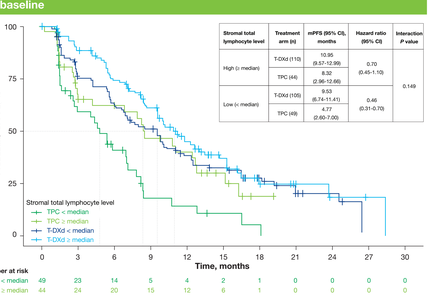
Median PFS was estimated by the Kaplan-Meier method, and the hazard ratio was calculated comparing the T-DXd and TPC arms in each biomarker-derived subgroup.

Figure 5. Association of tumor microenvironment immune features with (A) cORR and (B) hazard ratio for PFS



Dashed vertical lines in panel A show cORR in the HR+ ITT population.
[a]High and low were defined according to the median value.
[b]Not evaluated because cell density was zero in more than half of the patients.
[c]Hazard ratio for T-DXd vs TPC.

Figure 6. Probability of PFS according to levels of stromal total lymphocytes at baseline



Stromal total lymphocyte level	Treatment arm (n)	mPFS (95% CI), months	Hazard ratio (95% CI)	Interaction *P* value
High (≥ median)	T-DXd (110)	10.95 (9.57-12.99)	0.70 (0.49-1.10)	0.149
	TPC (44)	8.32 (2.96-12.66)		
Low (< median)	T-DXd (105)	9.53 (5.74-11.41)	0.46 (0.31-0.70)	
	TPC (49)	4.77 (2.60-7.00)		

Dashed vertical lines in panel A show cORR in the HR+ ITT population.
[a]High and low were defined according to the median value.
[b]Not evaluated because cell density was zero in more than half of the patients.
[c]Hazard ratio for T-DXd vs TPC.

Abbreviations

cORR, confirmed objective response rate; ctDNA, circulating tumor DNA; DDR, DNA damage repair; HER2, human epidermal growth factor receptor 2; HRR, homologous recombination repair; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intention-to-treat; *m*PFS, median PFS; NA, not available; ND, not detected; NK, natural killer; PFS, progression-free survival; RNA seq, RNA sequencing; TPC, treatment of physician's choice; T-DXd, trastuzumab deruxtecan.

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DESTINY-Breast04