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Exploratory biomarker analysis of trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) efficacy in human epidermal growth factor receptor 2–positive (HER2+) metastatic breast cancer (mBC) in DESTINY-Breast03 (DB-03)

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Disclosure Information

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William Jacot

I have the following relevant financial relationships to disclose:

Grant/Research support from: AstraZeneca, Daiichi Sankyo

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Participation on a data safety monitoring board or advisory board: AstraZeneca, Daiichi Sankyo, BMS, Novartis, Roche, Gilead, Eisai, Lilly France, MSD, Pfizer, Seagen

Background

- In DESTINY-Breast03 (DB-03; NCT03529110), T-DXd, a HER2-directed antibody-drug conjugate, demonstrated superior efficacy compared with T-DM1 in patients with HER2+ mBC that progressed on or after trastuzumab plus taxane[1]
  - During the second interim analysis (DCO July 25, 2022), T-DXd demonstrated clinically meaningful improvement versus T-DM1 with a mPFS of 28.8 months versus 6.8 months (HR, 0.33 [95% CI, 0.26-0.43]) and showed statistically significant overall survival
- T-DXd is approved for the treatment of patients with HER2+ mBC who have received a prior anti–HER2-based regimen in either the metastatic setting or in the neoadjuvant/adjuvant setting and developed disease recurrence during or within 6 months of completing therapy[2]
- The cytotoxic payload of T-DXd is a topoisomerase I inhibitor,[3] and molecular biomarkers of DNA damage and response and cell proliferation pathways may be useful as prognostic and predictive biomarkers[4,5]

OBJECTIVES

To investigate potential prognostic/predictive value of baseline genomic alterations with T-DXd versus T-DM1 treatment in patients with HER2+ mBC.

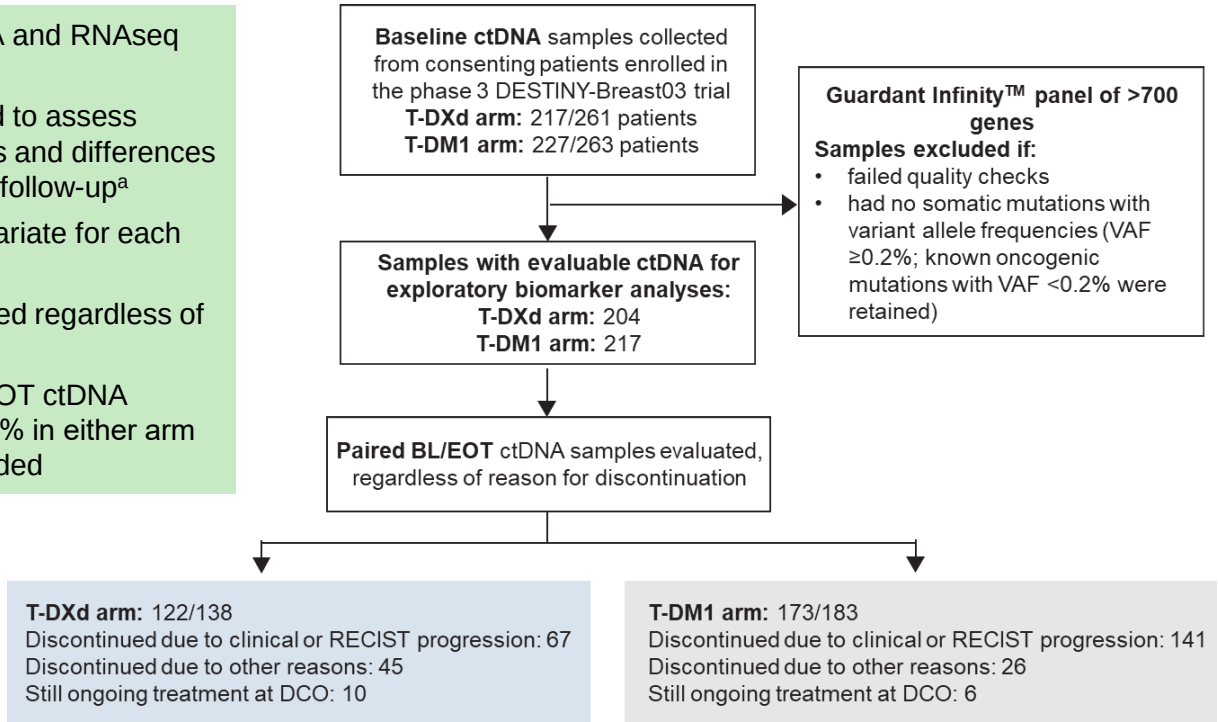
The emergence of genomic alterations at the end of treatment with T-DXd versus T-DM1 was also assessed.

DCO, data cutoff; HER2, human epidermal growth factor receptor 2; HR, hazard ratio, mBC, metastatic breast cancer; mPFS, median progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Hurvitz S et al. *Lancet*. 2023;401:105-117. 2. ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. Prescribing information. Daiichi Sankyo Inc; 2024. 3. Ogitani Y et al. *Clin Cancer Res*. 2016;22(20):5094-5108. 4. Neves Rebello Alves L et al. *Genes (Basel).* 2023;14(7):1364. 5. Thomas A et al. *Clin Cancer Res*. 2019;25(22):6581-6589.

Methods

- The analysis was done for both the ctDNA and RNAseq BEP
- Cox proportional hazards model was used to assess associations between BL biomarker status and differences in T-DXd versus T-DM1 mPFS at median follow-up[a]
- ctDNA tumor fraction was tested as a covariate for each Cox proportional hazards model
- Genetic alterations of interest were reported regardless of statistical significance
- For emerging mutations from paired BL/EOT ctDNA analysis, only genes with a prevalence ≥5% in either arm at baseline or end of treatment were included



BEP, biomarker-evaluable population; BL, baseline; ctDNA, circulating tumor DNA; DCO, data cutoff; EOT, end of treatment; mPFS, median progression-free survival; RECIST, response evaluation criteria in solid tumors; RNAseq, RNA sequencing; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan, VAF, varaint allele frequency.
[a]Median follow-up at DCO (July 25, 2022) of 28.4 months and 26.5 months in T-DXd and T-DM-1 arms, respectively.

Efficacy According to Baseline *HER2* Genomic Status

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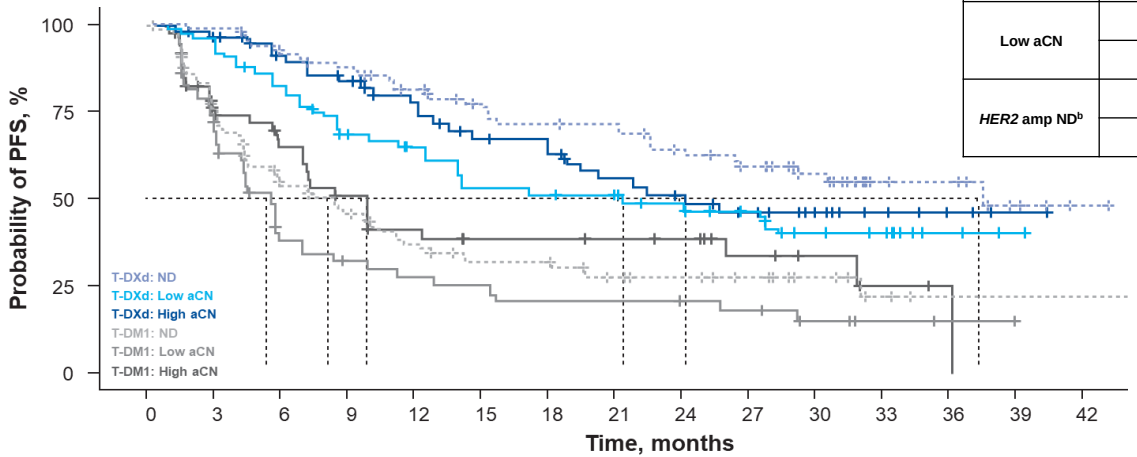
Status	Treatment Arm, n (%)[a]	ORR (95% CI), %	mPFS (95% CI), months	mPFS HR (95% CI)	mPFS Interaction *P* Value
High aCN	**T-DXd** 62 (30.4)	87.1 (76.1-94.3)	23.9 (18.0-NE)	0.46 (0.27-0.77)	0.53
	T-DM1 56 (25.8)	50.0 (36.3-63.7)	9.7 (6.8-25.7)		
Low aCN	**T-DXd** 59 (28.9)	81.4 (69.1-90.3)	21.1 (12.3-NE)	0.39 (0.24-0.61)	
	T-DM1 59 (27.2)	35.6 (23.6-49.1)	5.4 (3.0-6.8)		
HER2 amp ND[b]	**T-DXd** 83 (40.7)	77.1 (66.6-85.6)	37.3 (26.2-NE)	0.31 (0.21-0.48)	-
	T-DM1 102 (47.0)	31.4 (22.5-41.3)	8.1 (4.4-10.9)		



Number at risk

T-DXd: ND	83	82	74	69	61	54	50	47	41	35	25	11	10	3	1
T-DXd: Low aCN	59	55	47	37	33	27	26	23	19	16	11	8	3	1	0
T-DXd: High aCN	62	58	50	45	37	31	29	24	20	17	11	6	3	1	0
T-DM1: ND	102	69	48	38	30	24	22	18	16	13	7	3	1	1	1
T-DM1: Low aCN	59	36	19	15	12	11	9	9	8	7	4	2	1	0	0
T-DM1: High aCN	56	33	28	21	16	13	13	12	11	7	4	2	0	0	0

- Detection rate of *HER2* amplification was 56% (236/421 samples), including aneuploidy and focal *HER2* amplification
- Efficacy was comparable in the T-DXd arm regardless of high/low median *HER2* plasma aCN at BL. In the T-DM1 arm, mPFS and ORR were numerically higher in the *HER2* plasma high aCN subgroup vs the low aCN subgroup
- Patients without any *HER2* amplification detected in ctDNA (ND) tend to have lower ctDNA TF, which is positively prognostic,[1] as reflected by the efficacy in this subgroup

aCN, adjusted copy number; BL, baseline; ctDNA, circulating tumor DNA; *HER2*, human epidermal growth factor receptor 2; HR, hazard ratio; mPFS, median progression-free survival; ND, not detected; NE, not estimatable; ORR, objective response rate; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TF, tumor fraction.
[a]Percentages calculated using 204 and 217 as the denominators for T-DXd and T-DM1, respectively. [b]Not detected in samples with analyzable ctDNA.

1. Liu B et al. *Breast.* 2022;65:116-123

Association of Baseline Biomarkers and Hazard Ratio for PFS

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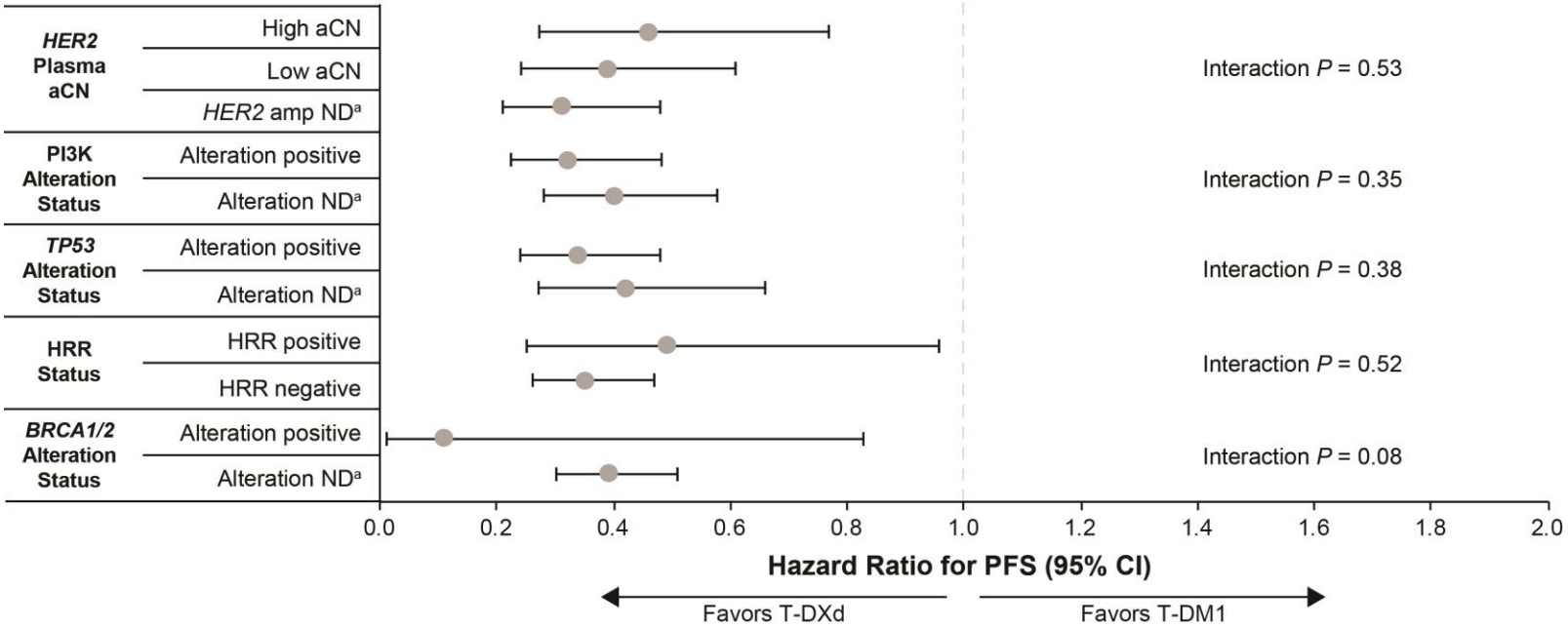
- T-DXd maintained superior clinical activity, as measured by HR for PFS, when compared with T-DM1, regardless of the presence of BL gene alterations



aCN, adjusted copy number; BL, baseline, *BRCA1/2*, breast cancer gene 1/2; *HER2*, human epidermal growth factor receptor 2; HR, hazard ratio; HRR, homologous recombination repair; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; ND, not detected; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; *TP53*, tumor protein 53.
[a]Not detected in samples with analyzable DNA.

Efficacy According to Baseline PI3K Biomarker Status

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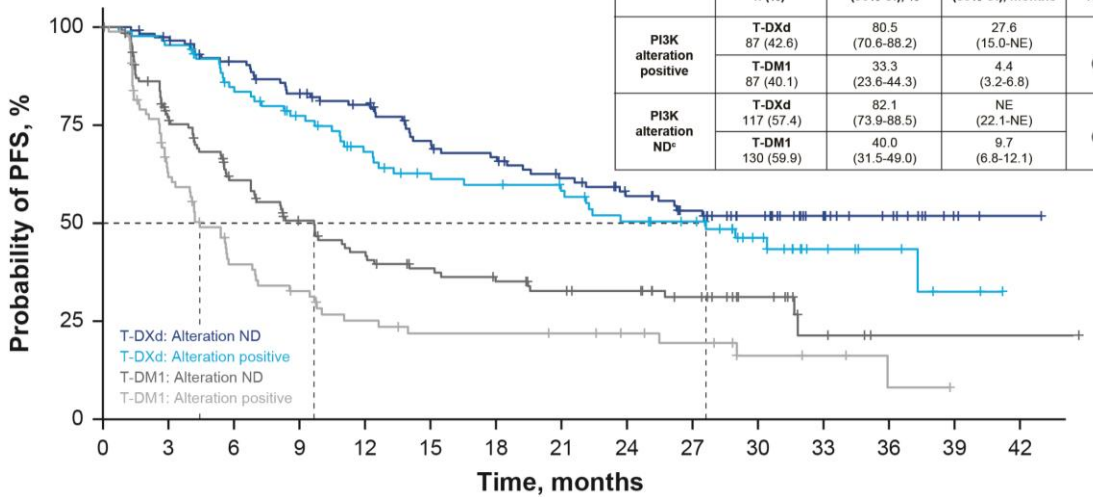
- T-DXd maintained superior clinical activity compared with T-DM1 regardless of the presence of PI3K pathway alterations[1,2,a]

Status	Treatment Arm, n (%)[b]	ORR (95% CI), %	mPFS (95% CI), months	mPFS HR (95% CI)	mPFS Interaction *P* Value
PI3K alteration positive	T-DXd 87 (42.6)	80.5 (70.6-88.2)	27.6 (15.0-NE)	0.32 (0.22-0.48)	0.35
	T-DM1 87 (40.1)	33.3 (23.6-44.3)	4.4 (3.2-6.8)		
PI3K alteration ND[c]	T-DXd 117 (57.4)	82.1 (73.9-88.5)	NE (22.1-NE)	0.40 (0.28-0.58)	
	T-DM1 130 (59.9)	40.0 (31.5-49.0)	9.7 (6.8-12.1)		



mPFS, median progression-free survival; ND, not detected; NE, not evaluable; ORR, objective response rate; PI3K, phosphoinositide 3-kinase; *PIK3CA,* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival; *PTEN*, phosphatase and tensin homolog; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]PI3K pathway alterations defined per the CAPItello-291 trial: activating mutations in *PIK3CA* and *AKT* and inactivating alterations (including deletions) in *PTEN* genes. [b]Percentages calculated using 204 and 217 as the denominators for T-DXd and T-DM1, respectively. [c]Not detected in samples with analyzable ctDNA.

1. FoundationOne CDx Technical Information (RAL-0003-24)- FoundationOne_CDx_Label_Technical_Info.pdf (www.foundationmedicine.com). 2. Turner NC et al. *N Engl J Med*. 2023;388:2058-2070.

PFS According to Baseline *TP53* Biomarker Status

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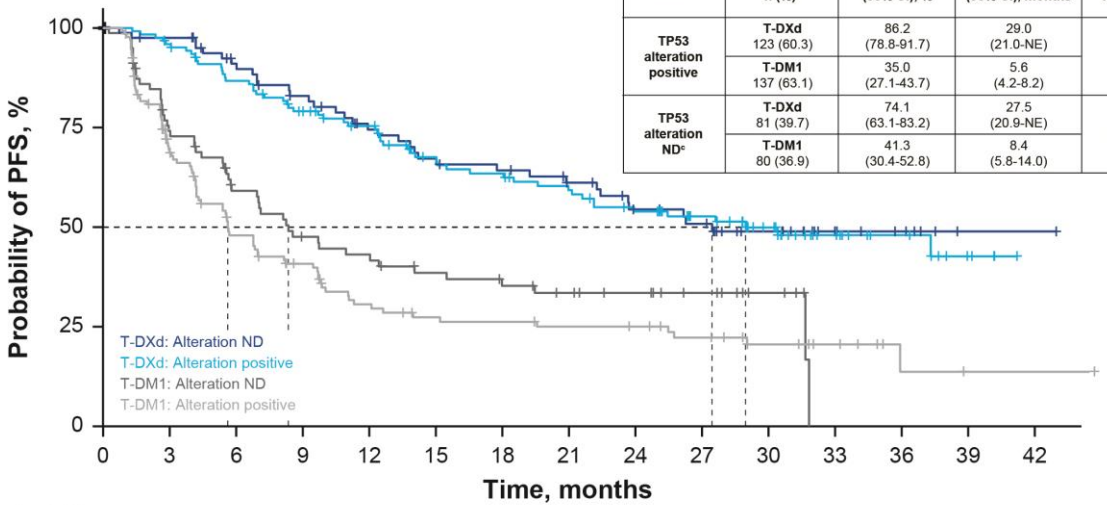
- T-DXd maintained superior clinical activity to T-DM1 regardless of the presence of *TP53* alterations[a]

Status	Treatment Arm, n (%)[b]	ORR (95% CI), %	mPFS (95% CI), months	mPFS HR (95% CI)	mPFS Interaction *P* Value
TP53 alteration positive	T-DXd 123 (60.3)	86.2 (78.8-91.7)	29.0 (21.0-NE)	0.34 (0.24-0.48)	0.38
	T-DM1 137 (63.1)	35.0 (27.1-43.7)	5.6 (4.2-8.2)		
TP53 alteration ND[c]	T-DXd 81 (39.7)	74.1 (63.1-83.2)	27.5 (20.9-NE)	0.42 (0.27-0.66)	
	T-DM1 80 (36.9)	41.3 (30.4-52.8)	8.4 (5.8-14.0)		



Number at risk															
T-DXd: Alteration ND	81	78	68	60	51	46	43	38	31	28	19	9	6	1	1
T-DXd: Alteration positive	123	117	103	91	80	66	62	56	49	40	28	16	10	4	0
T-DM1: Alteration ND	80	56	41	32	29	24	21	18	15	11	5	0	0	0	0
T-DM1: Alteration positive	137	82	54	42	29	24	23	21	20	16	10	7	2	1	1

Indel, insertion/deletion; mPFS, median progression-free survival; ND, not detected; NE, not evaluable; ORR, objective response rate; PFS, progression-free survival; SNV, single nucleotide variant; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; *TP53*, tumor protein 53.

[a]Included SNVs and indels, classified as loss of function according to oncoKB™. [b]Percentages calculated using 204 and 217 as the denominators for T-DXd and T-DM1, respectively. [c]Not detected in samples with analyzable ctDNA.

Efficacy According to Baseline HRR Status – Updated Results

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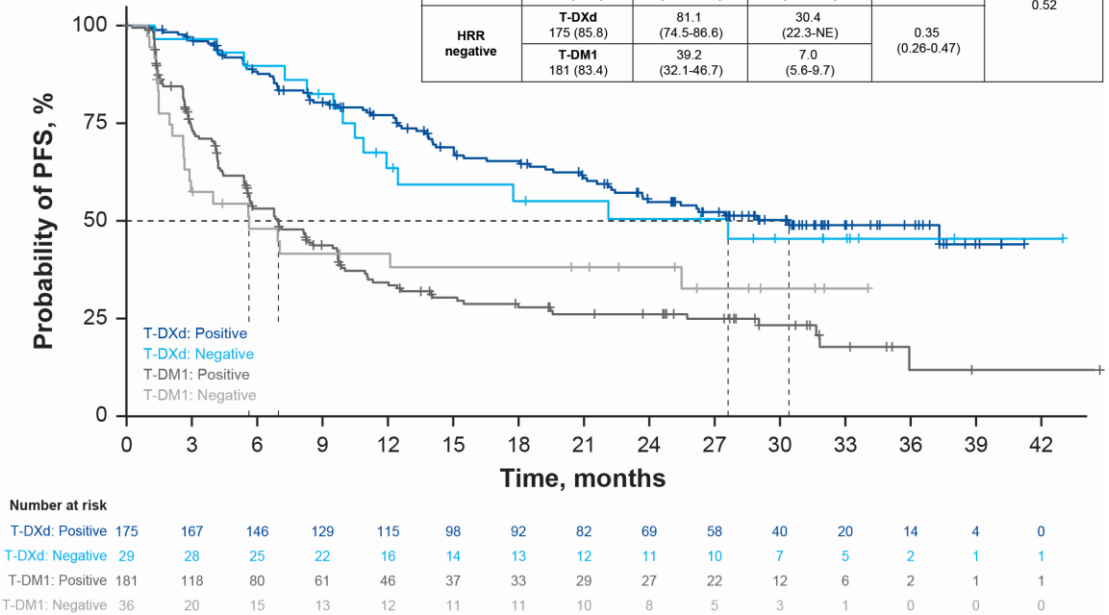
Status	Treatment Arm, n (%)[a]	ORR (95% CI), %	mPFS (95% CI), months	mPFS HR (95% CI)	mPFS Interaction *P* Value
HRR positive	T-DXd 29 (14.2)	82.8 (64.2-94.2)	27.6 (10.9-NE)	0.49 (0.25-0.96)	0.52
	T-DM1 36 (16.6)	27.8 (14.2-45.2)	5.6 (2.6-25.5)		
HRR negative	T-DXd 175 (85.8)	81.1 (74.5-86.6)	30.4 (22.3-NE)	0.35 (0.26-0.47)	
	T-DM1 181 (83.4)	39.2 (32.1-46.7)	7.0 (5.6-9.7)		



- HRD status in the **original analysis** was based on an algorithm employed by Guardant Health[1] which requires >10% ctDNA TF for HRD status detection; HRD includes many deletion cases, which are documented to be detectable only with higher ctDNA TF
- Higher ctDNA TF had a negative prognostic effect in the DB-03 dataset; it was therefore concluded that ctDNA TF was a confounding factor in the original analysis, specifically for HRD positive cases
- In an **updated analysis**, alterations in HRR genes,[2] excluding deletions, were analyzed to avoid the negative prognostic effect of high ctDNA TF as a confounding factor
- In the updated results, there are no obvious differences in PFS for the HRR positive vs HRR negative subgroups, in both arms
- ORRs remain similar with T-DXd regardless of HRR status, while with T-DM1, ORR trends worse in HRR positive populations

ctDNA, circulating tumor DNA; DB-03, DESTINY-Breast03; HR, hazard ratio; HRD, homologous recombination deficiency; HRR, homologous recombination repair; mPFS, median progression-free survival; ND, not detected; NE, not evaluable; ORR, objective response rate; PFS, progression-free survival; TF, tumor fraction; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TF, tumor fraction.

[a]Percentages calculated using 204 and 217 as the denominators for T-DXd and T-DM1, respectively.

[1]Safabakhsh et al. Presented at: American Society of Clinical Oncology Annual Meeting, June 2-6, 2023; Chicago, IL. Abstract 6601. [2]Carr TH, *Cancers (Basel)*. 2021 PMID: 34830984.

Efficacy According to Baseline *BRCA1/2* Status – Updated Results

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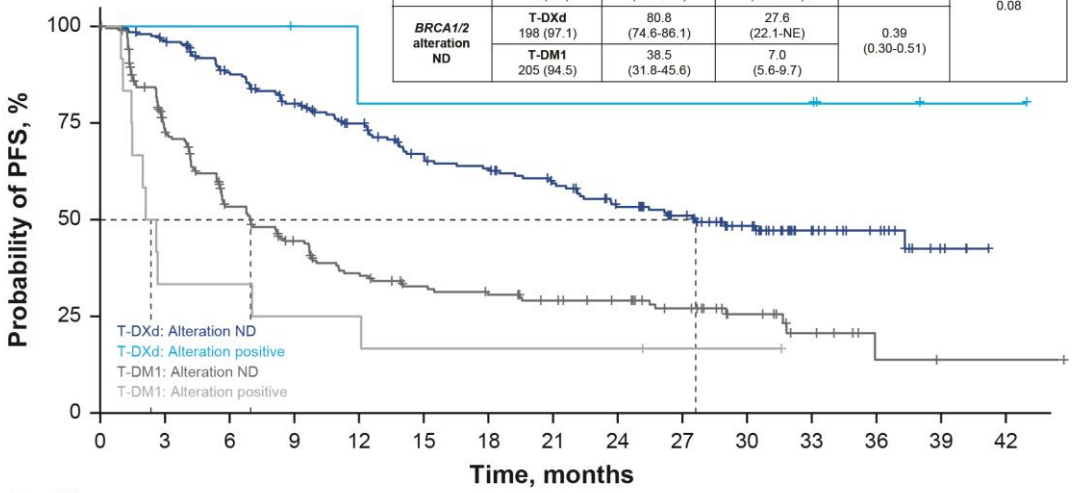
Status	Treatment Arm, n (%)[a]	ORR (95% CI), %	mPFS (95% CI), months	mPFS HR (95% CI)	mPFS Interaction *P* Value
BRCA1/2 alteration positive	T-DXd 6 (2.9)	100 (54.1-100)	NE (11.9-NE)	0.11 (0.01-0.83)	0.08
	T-DM1 12 (5.5)	16.7 (2.1-48.4)	2.4 (1.1-12.1)		
BRCA1/2 alteration ND	T-DXd 198 (97.1)	80.8 (74.6-86.1)	27.6 (22.1-NE)	0.39 (0.30-0.51)	
	T-DM1 205 (94.5)	38.5 (31.8-45.6)	7.0 (5.6-9.7)		



Number at risk															
T-DXd: Alteration ND	198	189	165	146	127	108	101	90	76	64	43	21	14	4	0
T-DXd: Alteration positive	6	6	6	5	4	4	4	4	4	4	4	4	2	1	1
T-DM1: Alteration ND	205	134	91	71	55	46	42	37	33	26	14	7	2	1	1
T-DM1: Alteration positive	12	4	4	3	3	2	2	2	2	1	1	0	0	0	0

- The **original analysis** included *BRCA1/2* deletion cases
- Reliable detection of deletion cases requires higher ctDNA TF[1] which, when not controlled for, is a confounding factor of negative prognosis
- Furthermore, as compared with small variants, deletions are more difficult to detect with confidence in ctDNA assays, made more challenging by variable plasma volumes in our samples
- It was therefore concluded to re-analyze the original data while excluding deletion cases to avoid these confounding factors
- In the **updated analysis**, *BRCA1/2* altered subgroups were defined only with SNV/indel cases (deletions excluded) to avoid potentially incorrectly assigned alterations and the negative prognostic effect of high ctDNA TF as a confounding factor
- The analysis resulted in very small subgroups; a larger sample size would be required for a more conclusive effect of *BRCA1/2* alterations on T-DXd efficacy

BRCA1/2, breast cancer gene 1/2; ctDNA, circulating tumor DNA; HR, hazard ratio; indel, insertion/deletion; mPFS, median progression-free survival; ND, not detected; NE, not estimatable; ORR, objective response rate; PFS, progression-free survival; TF, tumor fraction; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TF, tumor fraction.

[a]Percentages calculated using 204 and 217 as the denominators for T-DXd and T-DM1, respectively.

[1]Carr TH, Cancers (Basel). 2021 PMID: 34830984.

Emerging Mutations at End of Treatment

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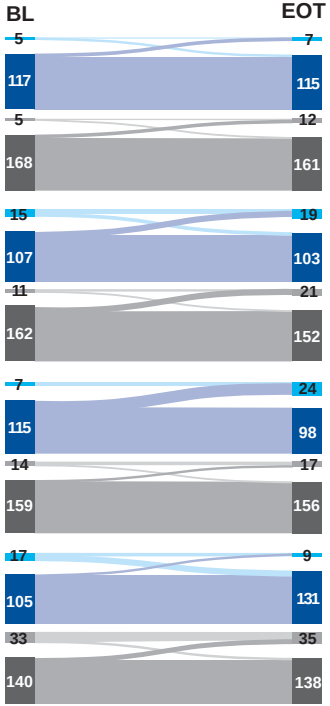
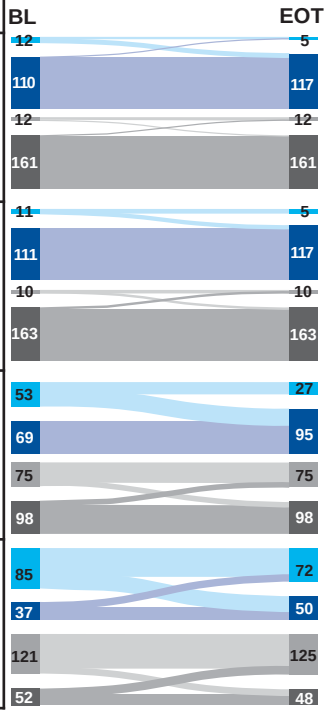
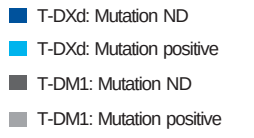
Gene	*P* value	Adjusted *P* value	Interaction *P* value
APC	0.754	0.918	0.577
	0.039	0.547	
ATM	0.424	0.742	0.549
	0.021	0.547	
CHEK2	<0.001	<0.001	0.065
	0.508	1.000	
HER2	0.021	0.191	0.223
	0.815	1.000	



Gene	*P* value	Adjusted *P* value	Interaction *P* value
GATA3	0.039	0.191	0.135
	1.000	1.000	
MED12	0.031	0.191	0.308
	1.000	1.000	
PIK3CA	<0.001	<0.001	0.014
	1.000	1.000	
TP53	0.041	0.191	0.284
	0.608	1.000	





- Emerging mutations from paired BL/EOT ctDNA analysis were assessed for genes with a prevalence ≥5% in either arm/timepoint
- *PIK3CA* mutations were retained after treatment in the T-DM1 arm compared with the T-DXd arm, where *PIK3CA* mutations were less frequent at EOT

APC, adenomatous polyposis coli; *ATM*, ataxia-telangiectasia mutated; BL, baseline; *CHEK2*, checkpoint kinase 2; ctDNA, circulating tumor DNA; EOT, end of treatment; *GATA3*, GATA binding protein 3; *HER2*, human epidermal growth factor receptor 2; *MED12*; mediator complex subunit 12; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; *TP53*, tumor protein 53.
Emerging mutations were assessed with a McNemar test and a generalized linear model, including tumor fraction as a covariate[1] and multi-test correction with the Benjamini-Hochberg procedure

[1]André F et al. *Ann Oncol.* 2025;36(1):54-64.

Emerging *TOP1* Mutations at Baseline and End of Treatment

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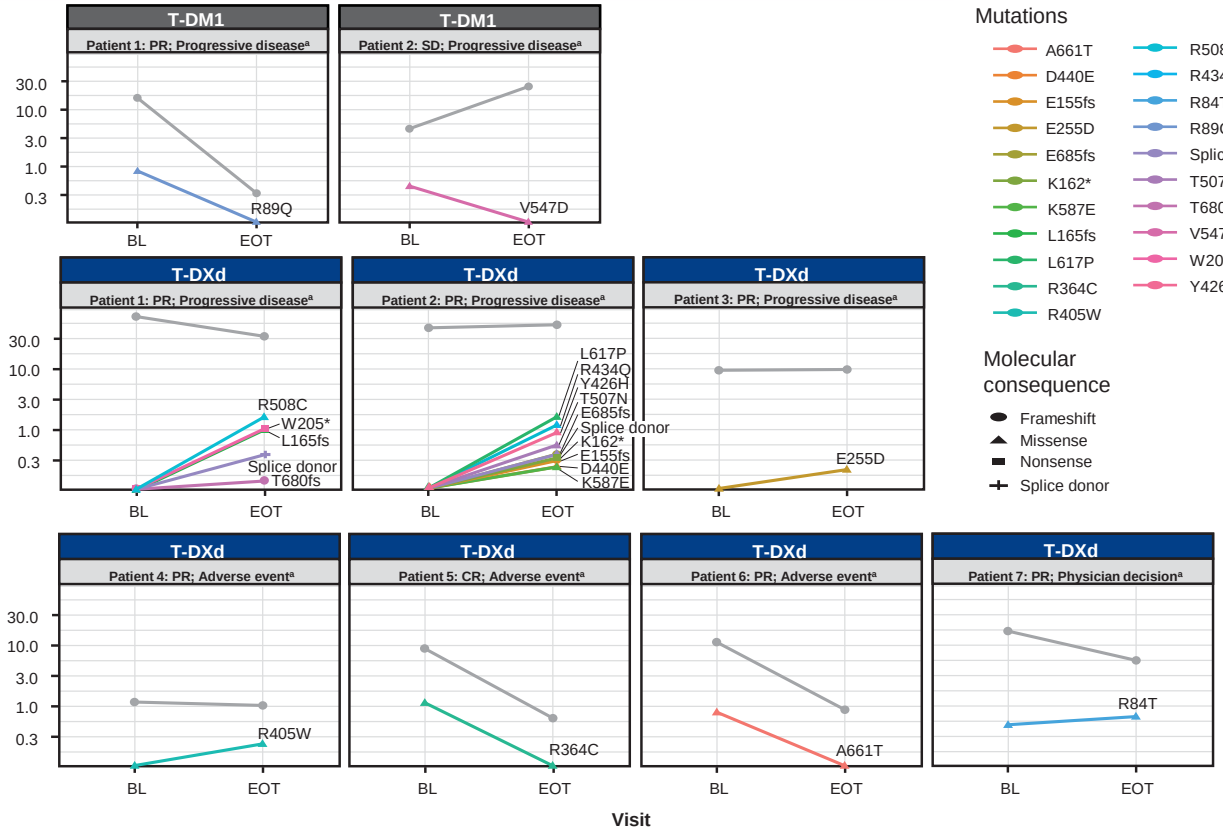

- *TOP1* SNV/indels at BL or EOT were reported regardless of prevalence and VAF
- Although present at low frequencies in both arms at BL and EOT (<5.0%), *TOP1* mutations appeared to emerge in 4 patients in the T-DXd arm; none were detected in the T-DM1 arm
- In the T-DXd arm, multiple emerging *TOP1* mutations were detected in 2 patients, who discontinued due to disease progression, with a BOR of PR
- All emerging *TOP1* mutations, except 1, have unknown significance relating to TOP1 function or inhibitor binding and span the N-terminal, core, and linker domains of TOP1

BOR, best overall response; BL, baseline; CR, complete response; EOT, end of treatment; indel, insertion/deletion; PR, partial response; SD, stable disease; SNV, single nucleotide variants; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; *TOP1*, topoisomerase 1; VAF, variant allele frequency.
Asterisk denotes translation termination. Grey line represents max VAF as tumor fraction.
[a]Confirmed BOR, reason for discontinuation.

Conclusions

- Based on this comprehensive analysis of patients from DB-03, genomic alterations at baseline were not identified to be predictive of efficacy of T-DXd compared to T-DM1
- T-DXd maintained superior activity compared with T-DM1 regardless of the presence of pre-defined detectable baseline genomic alterations relevant to mBC, including PI3K, *TP53,* HRR, and *BRCA1/2*
- Emergence of *TOP1* mutations after T-DXd treatment represents a potential mechanism of resistance in a limited number of patients from DB-03 (n = 4)
  - Due to the small number of cases and currently unknown impact of observed mutations on TOP1 function or DXd binding, additional datasets may be beneficial to further characterize the significance of this finding[1,2]

BRCA1/2, breast cancer gene 1/2; DB-03, Destiny-Breast03; DXd, deruxtecan; HRR, homologous recombination deficiency; mBC, metastatic breast cancer; PI3K, phosphoinositide 3-kinase; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; *TOP1*, topoisomerase 1; *TP53*, tumor protein 53.

1. Coates et al. *Cancer Disc*. 2021; 11 (10): 2436–2445.; 2. Occhiogrosso Abelman et al. *Cancer Re*s. 2024; 84 (6_Supplement): 3888.

Acknowledgements

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