Exploratory biomarker analysis of trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) in HER2-low/ultralow, hormone receptor–positive (HR+) metastatic breast cancer (mBC) in DESTINY-Breast06

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On behalf of the DESTINY-Breast06 investigators

Key takeaways

BACKGROUND

The presence of PI3K/AKT pathway, *ESR1*, and *BRCA1/2* mutations can inform treatment decision making for patients with mBC[1–3]

EXPLORATORY FINDINGS

In the **DESTINY-Breast06** biomarker-evaluable population, **T-DXd** demonstrated an **efficacy benefit** (PFS, confirmed ORR, and PFS2) compared with TPC **regardless of baseline PI3K/AKT pathway,* *ESR1*, or *BRCA1/2* mutation status**

CONCLUSION

Findings are consistent with those in the overall (intent-to-treat) **DESTINY-Breast06 population**[4] and further support T-DXd as an effective treatment across patients with HR+, HER2-low or HER2-ultralow mBC after ≥1 endocrine-based therapies

*Includes *AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function mutations

AKT, protein kinase B; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; mBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival; PFS2, second progression-free survival / time from randomization to second progression or death; PI3K, phosphoinositide 3-kinase; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

1. Dickinson K, et al. *JAMA Netw Open*. 2024;7:e2431722; 2. Mailliez A, et al. *Int J Cancer*. 2023;152:921–931; 3. Deluche E, et al. *Am Soc Clin Oncol Educ Book*. 2015:e2–7; 4. Bardia A, et al. *N Engl J Med*. 2024;391:2110–2122

Background

- **DESTINY-Breast06** (NCT04494425) is a randomized, open-label, Phase 3 study that demonstrated a **clinically meaningful PFS benefit with T-DXd vs TPC** for patients with HR+, HER2-low or HER2-ultralow mBC who had progressed after one or more endocrine-based therapies[1]
- Based on DESTINY-Breast06, **T-DXd received FDA and EMA approval** for patients who are not considered suitable for subsequent endocrine therapy as the next line of treatment[2,3]
- **PI3K/AKT pathway, *ESR1* and *BRCA1/2* mutations** are potentially actionable biomarkers that can inform treatment decision making in this setting[4–8]

OBJECTIVE: to report an exploratory ctDNA analysis of DESTINY-Breast06 evaluating clinical outcomes according to baseline genomic status (data cutoff: March 18, 2024)

AKT, protein kinase B; ctDNA, circulating tumor DNA; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; mBC, metastatic breast cancer; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

1. Bardia A, et al. *N Engl J Med*. 2024;391:2110–2122; 2. Fam-trastuzumab deruxtecan-nxki: highlights of prescribing information. 2025. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761139s032s035lbl.pdf (Accessed April 22, 2025); 3. Trastuzumab deruxtecan: summary of product characteristics. 2025. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf (Accessed May 1, 2025); 4. Dickinson K, et al. *JAMA Netw Open.* 2024;7:e2431722; 5. Mailliez A, et al. *Int J Cancer*. 2023;152:921–931; 6. Angus L, et al. *Nat Genet*. 2019;51:1450–1458; 7. Boscolo Bielo L, et al. *ESMO Open*. 2024;9:103731; 8. Deluche E, et al. *Am Soc Clin Oncol Educ Book*. 2015:e2–7

DESTINY-Breast06 study design and primary results

A randomized, multicenter, open-label, Phase 3 study[1,2]

Data cutoff: March 18, 2024

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)

HER2-low = 713
HER2-ultralow = 153

TPC (n=430)

Capecitabine (59.8%)
Nab-paclitaxel (24.4%)
Paclitaxel (15.8%)

Baseline characteristics*

- Median age ~58 years; ECOG PS ≥1 ~40%
- De-novo mBC ~31%; liver metastases ~67%; visceral disease ~85%; primary endocrine resistance† ~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)‡

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)§
- OS: data maturity ~40% at first interim analysis
- PFS2 (INV)
- Safety and tolerability

Exploratory endpoint

- Biomarkers

*As averaged across treatment groups in the ITT population; †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;[3] ‡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−); §the hazard ratio and its CI were estimated from an unstratified Cox proportional hazards model

BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; 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; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival / time from randomization to second progression or death; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

1. NCT04494425. Updated. April 2, 2025. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed May 1, 2025); 2. Bardia A, et al. *N Engl J Med*. 2024;391:2110–2122; 3. Cardoso F, et al. *Ann Oncol*. 2020;31:1623–1649

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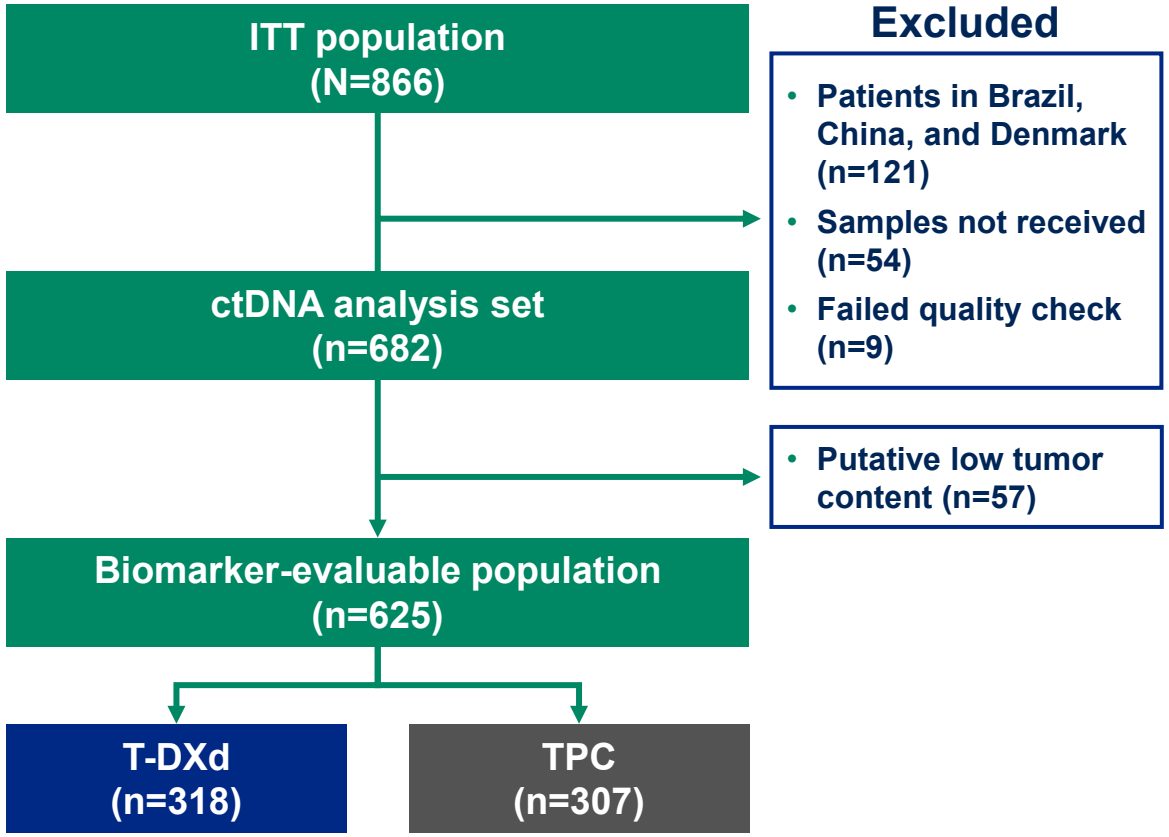
Methods

- **Blood samples** were collected at baseline, and ctDNA profiling conducted via GuardantOMNI™ 500-gene liquid biopsy assay
- **PI3K/AKT pathway** (*AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function), ***ESR1*** and ***BRCA1/2*** **mutations** were investigated
  - Both germline and somatic mutations in *BRCA1/2* were considered if there was evidence of prior actionability*
- In total, **625 patients** with evaluable ctDNA samples and putative tumor content comprised the biomarker-evaluable population†
- For each subgroup, **≥20 events were required** across arms to enable robust interpretation of clinical outcomes
- This was an exploratory analysis; as such, **no formal significance testing** was performed, and no corrections made for multiple testing



No corrections were made for tumor fraction; analysis was applied to baseline samples and the detection/non-detection of alterations only. Any reported gene deletions were not considered in this analysis
*Germline mutations in other genes were considered as variation of uncertain significance / illegible for any subsequent association analyses; †the biomarker-evaluable population excludes patients in Brazil, China, and Denmark, as local regulations in these countries restrict use of patient samples for genomic testing for exploratory purposes
AKT, protein kinase B; ctDNA, circulating tumor DNA; ITT, intent-to-treat; mBC, metastatic breast cancer; PI3K, phosphoinositide 3-kinase; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

Clinical outcomes in biomarker-evaluable and ITT populations

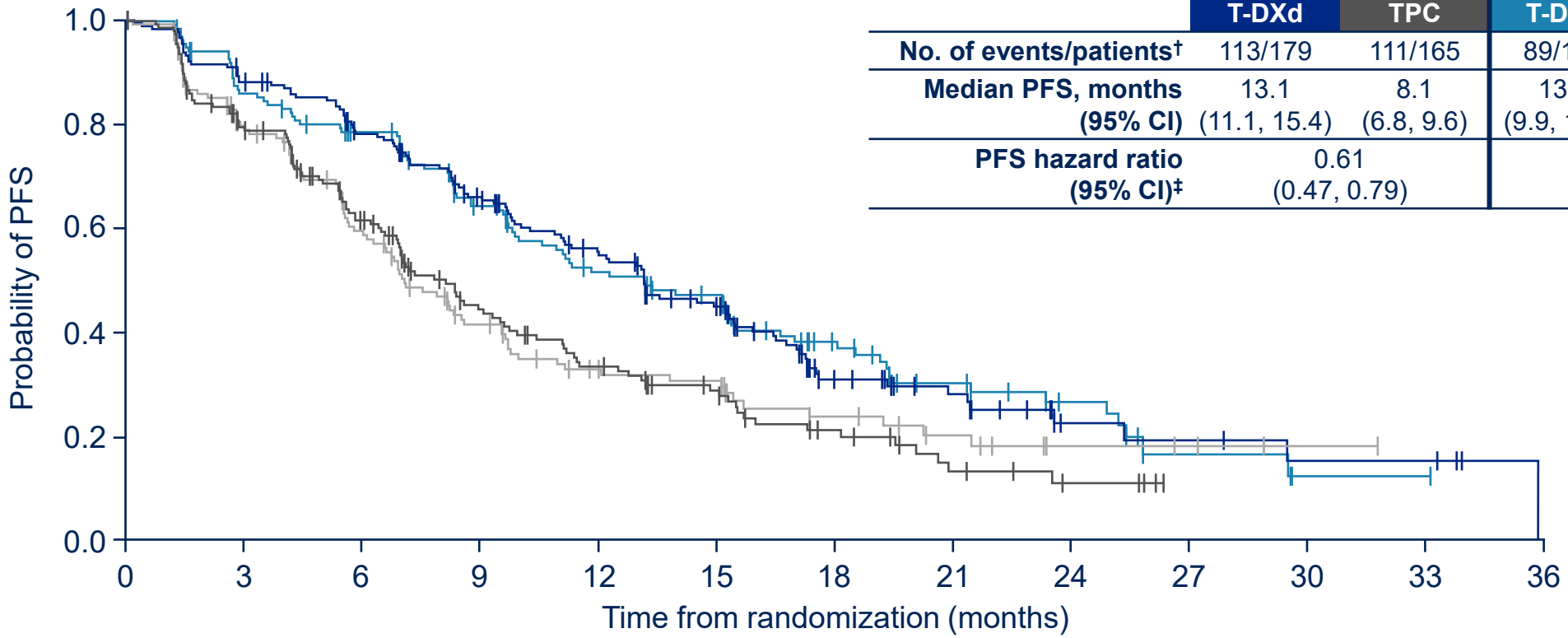
	Biomarker-evaluable population (n=625)		ITT population (N=866)[1]	
	T-DXd (n=318)	TPC (n=307)	T-DXd (n=436)	TPC (n=430)
Median PFS, months (95% CI)*	13.9 (12.3, 15.4)	8.2 (6.9, 9.5)	13.2 (12.0, 15.2)	8.1 (7.0, 9.0)
PFS hazard ratio (95% CI)*	0.63 (0.52, 0.76)		0.64 (0.54, 0.76)	
Confirmed ORR, % (95% CI)*	59.4 (53.8, 64.9)	33.9 (28.6, 39.5)	57.3 (52.5, 62.0)	31.2 (26.8, 35.8)

Overall, clinical outcomes (PFS and confirmed ORR) in the biomarker-evaluable population were consistent with the ITT population[1]

PFS hazard ratios and CIs were based on a Cox proportional hazards model with no stratification factors, and ties handled by Efron approach
*Assessed by BICR
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH−, in situ hybridization–negative; ITT, intent-to-treat; ORR, objective response rate; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy
1. Bardia A, et al. *N Engl J Med*. 2024;391:2110–2122

PFS (BICR) by baseline PI3K/AKT pathway* mutation status

PI3K/AKT pathway mutations were observed in 45.0% (n=281) of patients in the biomarker-evaluable population and were balanced across treatment groups



	WT		Mut	
	T-DXd	TPC	T-DXd	TPC
No. of events/patients†	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)‡	0.61 (0.47, 0.79)		0.65 (0.48, 0.87)	

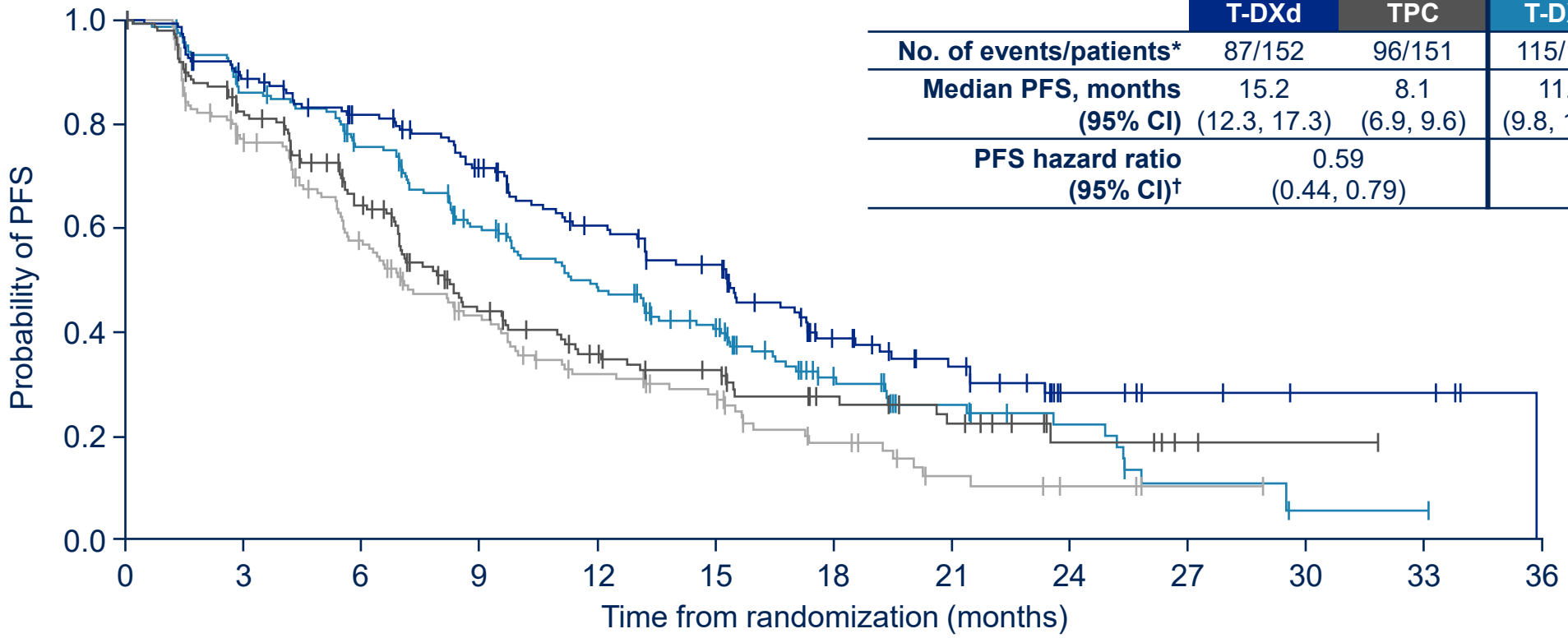
T-DXd improved PFS versus TPC regardless of PI3K/AKT pathway mutation status

Vertical lines indicate censored observations; CIs for median were derived based on Brookmeyer-Crowley method; BICR according to RECIST 1.1. *Includes *AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function mutations; †number of patients with mutation; ‡hazard ratios and CIs were based on a Cox proportional hazards model with no stratification factors, and ties handled by Efron approach (a hazard ratio <1 favored T-DXd vs TPC)
AKT, protein kinase B; BICR, blinded independent central review; CI, confidence interval; Mut, mutation; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; WT, wild type

PFS (BICR) by baseline *ESR1* mutation status

ESR1 mutations were observed in 51.5% (n=322) of patients in the biomarker-evaluable population and were balanced across treatment groups

	WT		Mut	
	T-DXd	TPC	T-DXd	TPC
No. of events/patients*	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)†	0.59 (0.44, 0.79)		0.64 (0.49, 0.83)	



T-DXd improved PFS versus TPC regardless of *ESR1* mutation status

Vertical lines indicate censored observations; CIs for median were derived based on Brookmeyer-Crowley method; BICR according to RECIST 1.1. *Number of patients with mutation; †hazard ratios and CIs were based on a Cox proportional hazards model with no stratification factors, and ties handled by Efron approach (a hazard ratio <1 favored T-DXd vs TPC)
BICR, blinded independent central review; CI, confidence interval; Mut, mutation; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; WT, wild type

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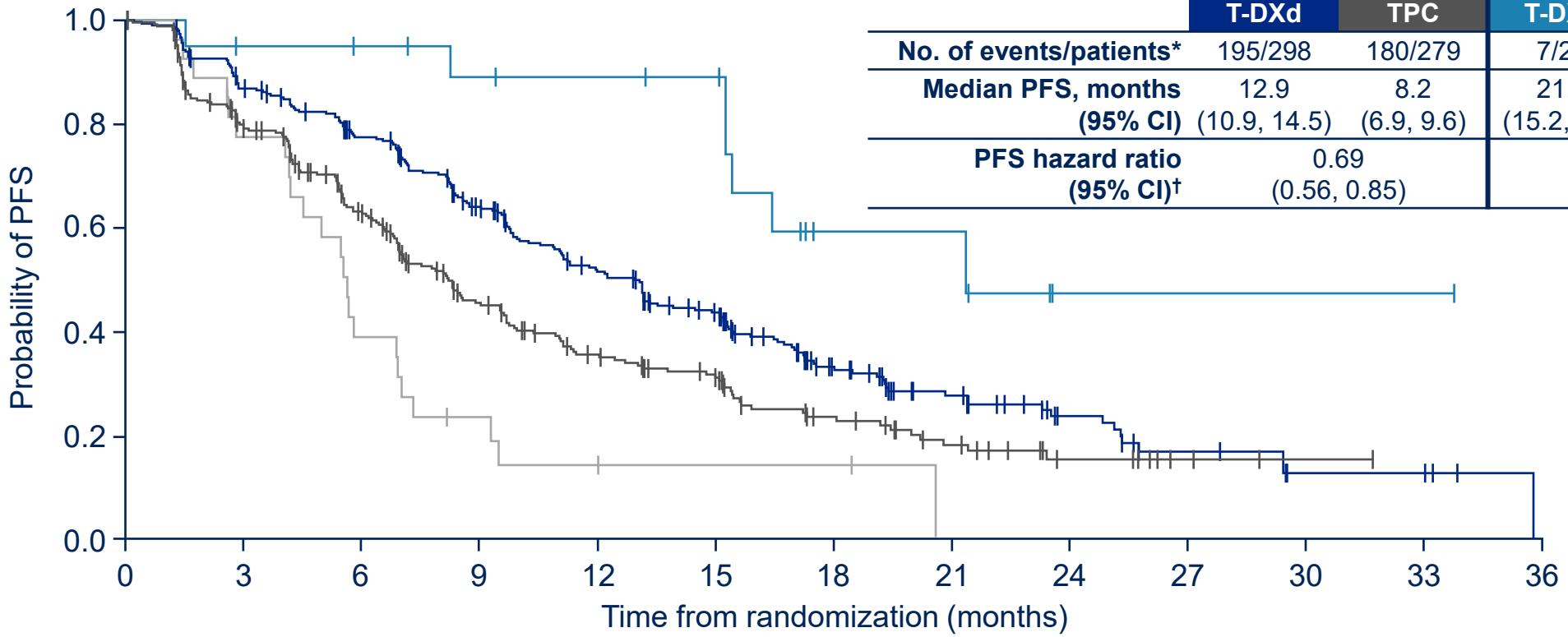
PFS (BICR) by baseline *BRCA1/2* mutation status

BRCA1/2 mutations were observed in 7.7% (n=48) of patients in the biomarker-evaluable population

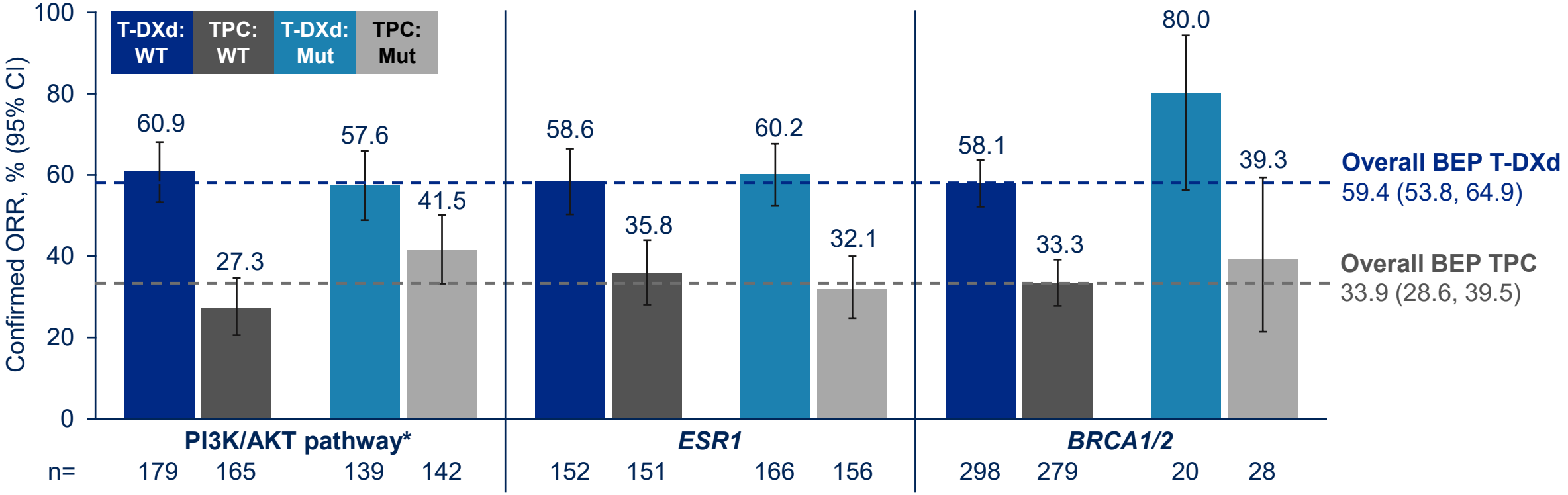


	WT		Mut	
	T-DXd	TPC	T-DXd	TPC
No. of events/patients*	195/298	180/279	7/20	23/28
Median PFS, months (95% CI)	12.9 (10.9, 14.5)	8.2 (6.9, 9.6)	21.4 (15.2, NE)	5.6 (4.1, 6.9)
PFS hazard ratio (95% CI)†	0.69 (0.56, 0.85)		0.14 (0.05, 0.33)	

T-DXd improved PFS versus TPC regardless of *BRCA1/2* mutation status; a potentially greater benefit with T-DXd was observed in the Mut subgroup (albeit with a small sample size)

Vertical lines indicate censored observations; CIs for median were derived based on Brookmeyer-Crowley method; BICR according to RECIST 1.1. *Number of patients with mutation; †hazard ratios and CIs were based on a Cox proportional hazards model with no stratification factors, and ties handled by Efron approach (a hazard ratio <1 favored T-DXd vs TPC). BICR, blinded independent central review; CI, confidence interval; Mut, mutation; NE, not evaluable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; WT, wild type

Confirmed ORR (BICR) by baseline biomarker status



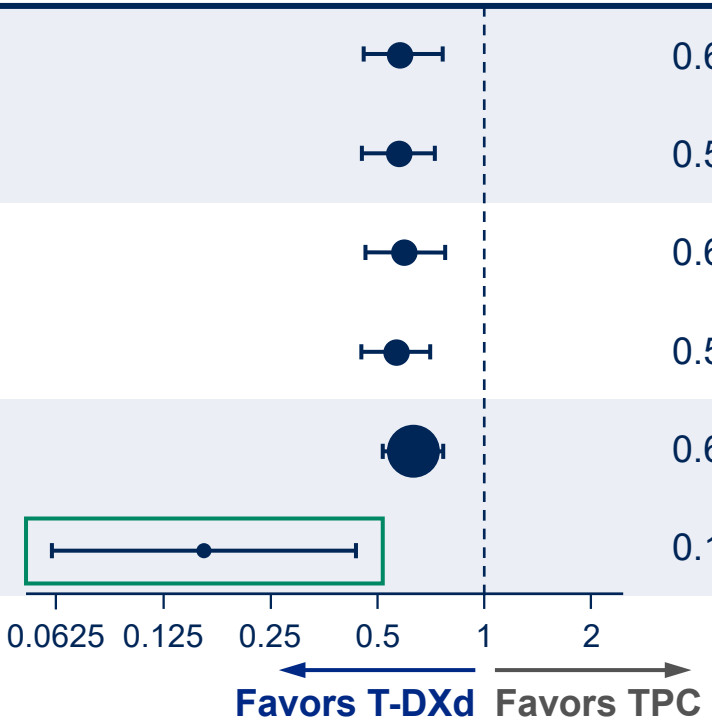
Confirmed ORR was improved with T-DXd versus TPC regardless of PI3K/AKT pathway, *ESR1,* or *BRCA1/2* mutation status

Confirmed ORR CIs were calculated using the Clopper-Pearson method; BICR 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]
*Includes *AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function mutations
AKT, protein kinase B; BEP, biomarker-evaluable population; BICR, blinded independent central review; CI, confidence interval; ITT, intent-to-treat; Mut, mutation; ORR, objective response rate; PI3K, phosphoinositide 3-kinase; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; WT, wild type

1. Bardia A, et al. *N Engl J Med*. 2024;391:2110–2122

PFS2 (INV) by baseline biomarker status

		No. of events/patients		Median PFS2, months (95% CI)		Hazard ratio (95% CI)†
		T-DXd	TPC	T-DXd	TPC	
PI3K/AKT pathway*	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)



Delay in PFS2 was in favor of T-DXd versus TPC regardless of PI3K/AKT pathway, *ESR1,* or *BRCA1/2* mutation status; a potentially greater benefit with T-DXd was observed in the *BRCA1/2* Mut subgroup (albeit with a small sample size)

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 calculated using the Kaplan-Meier technique; CIs for median were derived based on Brookmeyer-Crowley method. *Includes *AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function mutations; †the hazard ratio and CI were calculated using a Cox proportional hazards model with no stratification factors, and ties handled by Efron approach (a hazard ratio <1 favored T-DXd vs TPC)
AKT, protein kinase B; CI, confidence interval; INV, investigator; Mut, mutation; NE, not evaluable; PFS2, second progression-free survival / time from randomization to second progression or death; PI3K, phosphoinositide 3-kinase; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; WT, wild type

Conclusions

- In the DESTINY-Breast06 biomarker-evaluable population, T-DXd demonstrated a greater PFS benefit compared with TPC regardless of baseline PI3K/AKT pathway,* *ESR1*, or *BRCA1/2* mutation status
  - PI3K/AKT pathway (median PFS **13.1–13.2 mo [T-DXd]** vs **7.1–8.1 mo [TPC]**; hazard ratio: 0.61–0.65)†
  - *ESR1* (median PFS **11.3–15.2 mo [T-DXd]** vs **7.0–8.1 mo [TPC]**; hazard ratio: 0.59–0.64)†
  - *BRCA1/2* (median PFS **12.9–21.4 mo [T-DXd]** vs **5.6–8.2 mo [TPC]**; hazard ratio: 0.14–0.69)†
- ORR and 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 compared with all other subgroups (albeit with a small sample size)

Findings in the biomarker-evaluable population were consistent with those in the ITT population[1] and provide evidence that T-DXd is an effective treatment across patients with HR+, HER2-low or HER2-ultralow mBC after ≥1 endocrine-based therapies regardless of PIK3/AKT pathway,* *ESR1* or *BRCA1/2* mutation status

*Includes *AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function mutations; †median PFS and hazard ratio range includes WT and Mut data
AKT, protein kinase B; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; Mut, mutation; ORR, objective response rate; PFS, progression-free survival; PFS2, second progression-free survival / time from randomization to second progression or death; PI3K, phosphoinositide 3-kinase; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; WT, wild type

1. Bardia A, et al. *N Engl J Med*. 2024;391:2110–2122

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- **Study site staff for their contributions**
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Baseline characteristics

	PI3K/AKT pathway*				*ESR1*				*BRCA1/2*			
	WT		Mut		WT		Mut		WT		Mut	
	T-DXd (n=179)	TPC (n=165)	T-DXd (n=139)	TPC (n=142)	T-DXd (n=152)	TPC (n=151)	T-DXd (n=166)	TPC (n=156)	T-DXd (n=298)	TPC (n=279)	T-DXd (n=20)	TPC (n=28)
Median age, years	58.0	57.0	60.0	57.0	58.0	57.0	59.5	57.0	59.0	57.0	57.5	55.5
Female, n (%)	179 (100)	165 (100)	139 (100)	141 (99.3)	152 (100)	151 (100)	166 (100)	155 (99.4)	298 (100)	278 (99.6)	20 (100)	28 (100)
Race, n (%)												
White	116 (64.8)	101 (61.2)	79 (56.8)	79 (55.6)	93 (61.2)	84 (55.6)	102 (61.4)	96 (61.5)	185 (62.1)	166 (59.5)	10 (50.0)	14 (50.0)
Asian	40 (22.3)	40 (24.2)	42 (30.2)	50 (35.2)	41 (27.0)	50 (33.1)	41 (24.7)	40 (25.6)	72 (24.2)	79 (28.3)	10 (50.0)	11 (39.3)
Black or African American	1 (0.6)	0	2 (1.4)	1 (0.7)	2 (1.3)	0	1 (0.6)	1 (0.6)	3 (1.0)	1 (0.4)	0	0
Other	4 (2.3)	4 (2.4)	1 (0.7)	2 (1.4)	0	2 (1.3)	5 (3.0)	4 (2.6)	5 (1.6)	6 (2.2)	0	0
NR	18 (10.1)	20 (12.1)	15 (10.8)	10 (7.0)	16 (10.5)	15 (9.9)	17 (10.2)	15 (9.6)	33 (11.1)	27 (9.7)	0	3 (10.7)
Metastasis, n (%)												
Liver	132 (73.7)	110 (66.7)	97 (69.8)	102 (71.8)	101 (66.4)	100 (66.2)	128 (77.1)	112 (71.8)	218 (73.2)	189 (67.7)	11 (55.0)	23 (82.1)
Bone only	2 (1.1)	5 (3.0)	4 (2.9)	4 (2.8)	1 (0.7)	3 (2.0)	5 (3.0)	6 (3.8)	5 (1.7)	9 (3.2)	1 (5.0)	0
Visceral	161 (89.9)	142 (86.1)	124 (89.2)	130 (91.5)	133 (87.5)	136 (90.1)	152 (91.6)	136 (87.2)	269 (90.3)	245 (87.8)	16 (80.0)	27 (96.4)
Endocrine resistance†												
Primary‡	51 (28.5)	47 (28.5)	38 (27.3)	46 (32.4)	60 (39.5)	60 (39.7)	29 (17.5)	33 (21.2)	87 (29.2)	83 (29.7)	2 (10.0)	10 (35.7)
Secondary§	128 (71.5)	116 (70.3)	101 (72.7)	96 (67.6)	92 (60.5)	90 (59.6)	137 (82.5)	122 (78.2)	211 (70.8)	195 (69.9)	18 (90.0)	17 (60.7)

*Includes *AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function mutations; †missing data, n: PI3K/AKT pathway, WT TPC = 2 (1.2%); *ESR1* Mut TPC = 1 (0.6%); *ESR1* WT TPC = 1 (0.7%); *BRCA1/2* Mut TPC = 1 (3.6%); *BRCA1/2* WT TPC = 1 (0.4%); ‡defined as relapse while on the first 2 years of adjuvant ET, or progressive disease within the first 6 months of first-line ET for mBC, while on ET;[1] §defined as relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or progressive disease ≥6 months after initiating ET for mBC while on ET[1]

AKT, protein kinase B; ET, endocrine therapy; mBC, metastatic breast cancer; Mut, mutation; NR, not reported; PI3K, phosphoinositide 3-kinase; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; WT, wild type

1. Cardoso F, et al. *Ann Oncol*. 2020;31:1623–1649

Prior therapies

	PI3K/AKT pathway*				*ESR1*				*BRCA1/2*			
	WT		Mut		WT		Mut		WT		Mut	
	T-DXd (n=179)	TPC (n=165)	T-DXd (n=139)	TPC (n=142)	T-DXd (n=152)	TPC (n=151)	T-DXd (n=166)	TPC (n=156)	T-DXd (n=298)	TPC (n=279)	T-DXd (n=20)	TPC (n=28)
Number of prior lines of ET, n (%)												
Median (range)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–3)
1	30 (16.8)	33 (20.1)	19 (13.7)	21 (14.8)	36 (23.7)	38 (25.3)	13 (7.8)	16 (10.3)	46 (15.4)	50 (18.0)	3 (15.0)	4 (14.3)
2	110 (61.5)	109 (66.5)	97 (69.8)	96 (67.6)	95 (62.5)	93 (62.0)	112 (67.5)	112 (71.8)	198 (66.4)	182 (65.5)	9 (45.0)	23 (82.1)
≥3	39 (21.8)	22 (13.4)	23 (16.5)	25 (17.6)	21 (13.8)	19 (12.7)	41 (24.7)	28 (17.9)	54 (18.1)	46 (16.5)	8 (40.0)	1 (3.6)
ET + targeted therapy, n (%)												
ET with CDK4/6i	170 (95.0)	153 (92.7)	125 (89.9)	139 (97.9)	142 (93.4)	142 (94.0)	153 (92.2)	150 (96.2)	278 (93.3)	266 (95.3)	17 (85.0)	26 (92.9)
ET with mTORi	61 (34.1)	42 (25.5)	31 (22.3)	43 (30.3)	41 (27.0)	34 (22.5)	51 (30.7)	51 (32.7)	86 (28.9)	75 (26.9)	6 (30.0)	10 (35.7)
ET with PIK3CAi	4 (2.2)	1 (0.6)	19 (13.7)	8 (5.6)	11 (7.2)	5 (3.3)	12 (7.2)	4 (2.6)	21 (7.0)	9 (3.2)	2 (10.0)	0
ET with PARPi	0	2 (1.2)	2 (1.4)	2 (1.4)	1 (0.7)	0	1 (0.6)	4 (2.6)	2 (0.7)	3 (1.1)	0	1 (3.6)
ET with other	6 (3.4)	5 (3.0)	7 (5.0)	3 (2.1)	4 (2.6)	3 (2.0)	9 (5.4)	5 (3.2)	13 (4.4)	7 (2.5)	0	1 (3.6)
Targeted therapy (monotherapy or combination), n (%)	173 (96.6)	156 (94.5)	127 (91.4)	140 (98.6)	144 (94.7)	145 (96.0)	156 (94.0)	151 (96.8)	283 (95.0)	270 (96.8)	17 (85.0)	26 (92.9)
Adjuvant/neoadjuvant setting treatment(s), n (%)	120 (67.0)	101 (61.2)	87 (62.6)	90 (63.4)	111 (73.0)	101 (66.9)	96 (57.8)	90 (57.7)	199 (66.8)	174 (62.4)	8 (40.0)	17 (60.7)
Cytotoxic chemotherapy	91 (50.8)	77 (46.7)	65 (46.8)	76 (53.5)	86 (56.6)	76 (50.3)	70 (42.2)	77 (49.4)	151 (50.7)	137 (49.1)	5 (25.0)	16 (57.1)

Values are reported for prior therapies in the metastatic setting unless otherwise specified. *Includes *AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function mutations
AKT, protein kinase B; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; mTORi, mammalian target of rapamycin inhibitor; Mut, mutation; PARPi, poly (ADP-ribose) polymerase inhibitor; PIK3CAi, PIK3CA inhibitor; PI3K, phosphoinositide 3-kinase; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; WT, wild type

Safety outcomes by baseline biomarker status

Event, n (%)	PI3K/AKT pathway*				*ESR1*				*BRCA1/2*			
	WT		Mut		WT		Mut		WT		Mut	
	T-DXd (n=177)	TPC (n=162)	T-DXd (n=139)	TPC (n=141)	T-DXd (n=151)	TPC (n=148)	T-DXd (n=165)	TPC (n=155)	T-DXd (n=296)	TPC (n=276)	T-DXd (n=20)	TPC (n=27)
Grade 3 AEs	87 (49.2)	69 (42.6)	62 (44.6)	67 (47.5)	78 (51.7)	63 (42.6)	71 (43.0)	73 (47.1)	138 (46.6)	128 (46.4)	11 (55.0)	8 (29.6)
Grade 4 AEs	10 (5.6)	11 (6.8)	7 (5.0)	7 (5.0)	8 (5.3)	9 (6.1)	9 (5.5)	9 (5.8)	17 (5.7)	16 (5.8)	0	2 (7.4)
AEs leading to treatment discontinuation	22 (12.4)	17 (10.5)	18 (12.9)	11 (7.8)	19 (12.6)	8 (5.4)	21 (12.7)	20 (12.9)	35 (11.8)	26 (9.4)	5 (25.0)	2 (7.4)
SAEs	29 (16.4)	26 (16.0)	28 (20.1)	33 (23.4)	33 (21.9)	24 (16.2)	24 (14.5)	35 (22.6)	53 (17.9)	58 (21.0)	4 (20.0)	1 (3.7)
TRAEs with outcome of death	1 (0.6)	0	0	0	1 (0.7)	0	0	0	1 (0.3)	0	0	0

Data reported in the safety analysis set (defined as all patients who received at least one dose of study treatment)
*Includes *AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function mutations
AE, adverse event; AKT, protein kinase B; Mut, mutation; PI3K, phosphoinositide 3-kinase; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; TRAE, treatment-related adverse event; WT, wild type

DESTINY-Breast06

Plain language summary

What does this research tell us?

The presence or absence of certain genetic alterations (eg PI3K/AKT pathway, *ESR1*, *BRCA1,* or *BRCA2* mutations*)* in **metastatic breast cancer (mBC)** can help to guide the type of treatment a patient receives.[1–3] Exploratory analyses from the Phase 3 **DESTINY-Breast06 trial** showed that with or without these mutations, **trastuzumab deruxtecan (T-DXd) treatment** appeared to be better than **physician's choice of chemotherapy (TPC)** for patients who had a type of **mBC** with hormone receptors for estrogen and/or progesterone (hormone receptor–positive) and low or very low levels of a protein called HER2 (HER2-low or HER2-ultralow)

Who does this research impact?

These **exploratory results will support physicians in determining which patients with hormone receptor–positive, HER2-low or HER2-ultralow mBC may be suitable for T-DXd treatment** after they have received at least one hormone-based (endocrine) therapy

What does this mean for patients right now?

Based on the results from **DESTINY-Breast06**, T-DXd was approved in the US and EU for patients with hormone receptor–positive, HER2-low or HER2-ultralow mBC.[4,5] These exploratory results show that **patients had better clinical outcomes when given T-DXd compared with TPC** whether or not their cancer cells had **PI3K/AKT pathway,* *ESR1, BRCA1,* or *BRCA2* mutations**

*Includes *AKT1* and *PIK3CA* activating mutations, or *PTEN* loss-of-function mutations

AKT, protein kinase B; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; PI3K, phosphoinositide 3-kinase; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

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