Efficacy and safety of trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) by pace of disease progression on prior endocrine-based therapy: additional analysis from DESTINY-Breast06

LB1-04

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On behalf of the DESTINY-Breast06 investigators

Disclosures

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DESTINY-Breast06 study design and primary results

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

Data cutoff: March 18, 2024

Patient population

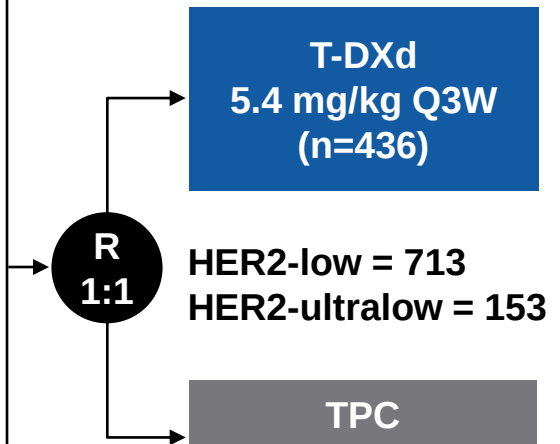
- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) **OR** HER2-ultralow (IHC 0 with membrane staining) status
- Chemotherapy naïve in the mBC setting

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**



Baseline characteristics*

- Median age **58 years**; ECOG PS ≥1 **~42%**
- **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<0.0001)†

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<0.0001)‡
- OS
  - Data maturity ~40% at first IA; early trend favoring T-DXd in ITT
- **PFS2 (INV)**
- Safety and tolerability

*As averaged across treatment groups in the ITT population; †the hazard ratio and its CI was 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 was 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; IA, interim analysis; 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; SOC, standard of care; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, physician's choice of chemotherapy

1. Curigliano G, et al. Oral presentation at ASCO 2024 (Abstract LBA1000); 2. NCT04494425. Updated. October 17, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed October 23, 2024)

Objectives

Investigate the benefit of T-DXd in patients with different responses to ET*

Time to progression on 1L ET + CDK4/6i; primary/secondary endocrine resistance

Assess the efficacy of subsequent therapies post progression on T-DXd/TPC

Time from randomization to second progression or death (PFS2)

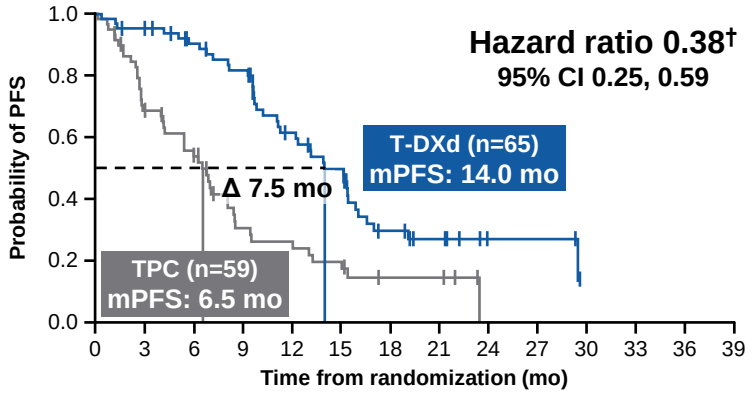
Understand the benefit of T-DXd in patients with varying disease burdens*

Baseline tumor extent and location

*Exploratory post-hoc analyses
1L, first line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; PFS2, second progression-free survival / time from randomization to second progression or death; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

PFS by time to progression on 1L ET + CDK4/6i and endocrine resistance

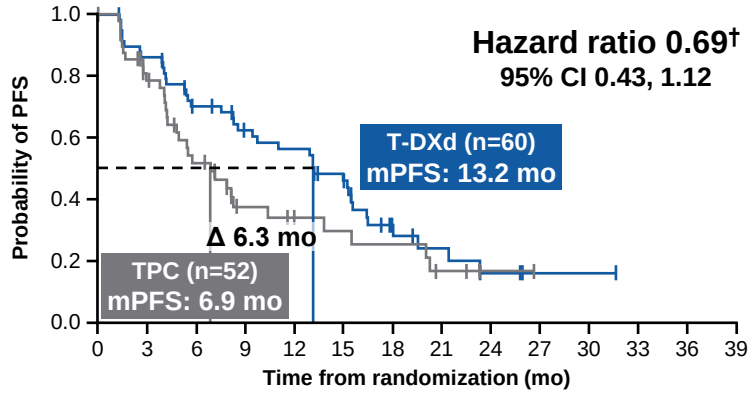
<6-mo 1L TTP*



Number at risk

T-DXd	65	61	53	47	32	25	12	8	3	3	0
TPC	59	38	30	14	12	9	4	4	0	0	0

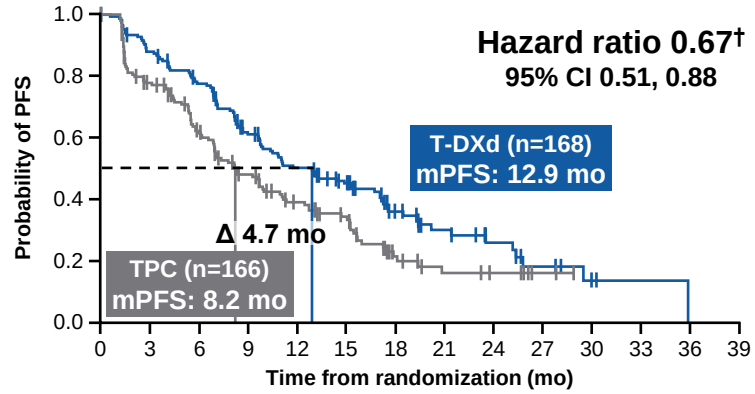
6–12-mo 1L TTP*



Number at risk

T-DXd	60	50	38	31	28	20	9	6	3	1	1	0
TPC	52	34	21	11	8	7	6	3	1	0	0	0

>12-mo 1L TTP*



Number at risk

T-DXd	168	146	125	94	74	59	28	17	11	6	2	1	0
TPC	166	114	86	62	44	33	14	8	6	2	0	0	0

	Primary endocrine resistance‡		Secondary endocrine resistance‡	
	T-DXd (n=128)	TPC (n=140)	T-DXd (n=308)	TPC (n=288)
mPFS, mo (95% CI)	12.4 (10.3, 15.2)	6.6 (5.4, 7.4)	13.2 (12.0, 15.5)	9.5 (8.0, 11.1)
PFS hazard ratio (95% CI)	0.57 (0.42, 0.77)†		0.68 (0.55, 0.84)†	

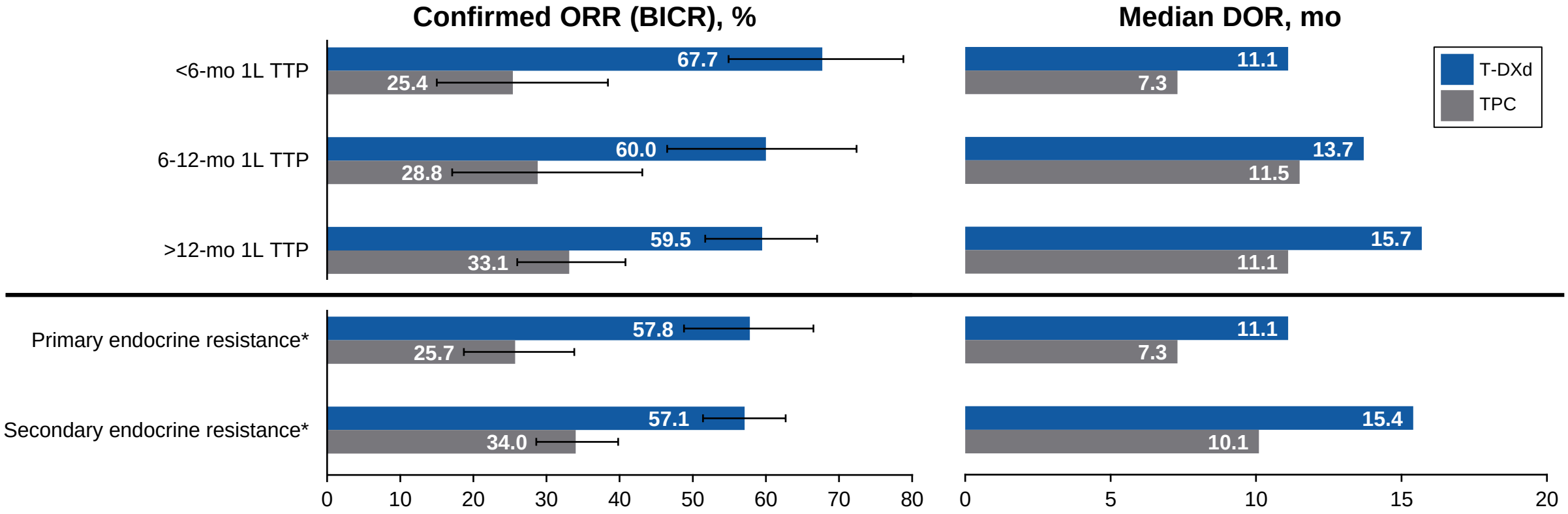
T-DXd improved PFS vs TPC regardless of time to progression on 1L ET + CDK4/6i or type of endocrine resistance

*TTP analysis included 570 patients with PD on prior 1L ET + CDK4/6i (65.8% of the ITT population); †the hazard ratio and its CI were estimated from an unstratified Cox proportional hazards model; ‡endocrine resistance assessed by investigators per 5th ESO-ESMO advanced breast cancer guidelines. Primary endocrine resistance was defined as relapse in the first 2 years of adjuvant ET, or PD <6 mo of 1L ET for mBC. Secondary (acquired) endocrine resistance was defined as relapse after the first 2 years on adjuvant ET, or relapse within 12 mo of completing adjuvant ET, or PD >6 mo after initiating ET for mBC[1]

1L, first line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ESO-ESMO, European School of Oncology-European Society for Medical Oncology; ET, endocrine therapy; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; (m)PFS, (median) progression-free survival; PD, progressive disease; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; TTP, time to progression

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

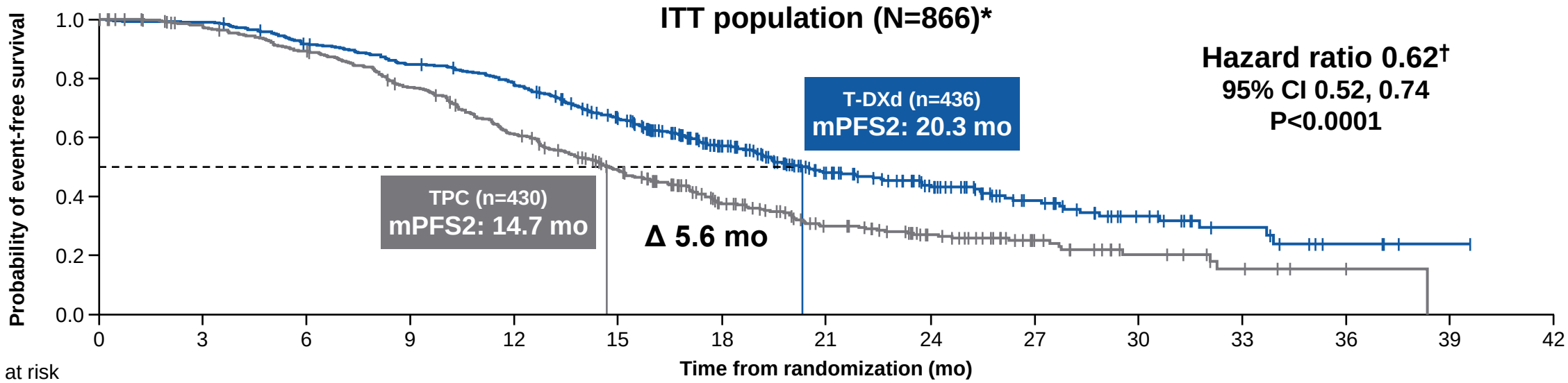
ORR and DOR by time to progression on 1L ET + CDK4/6i and endocrine resistance



T-DXd improved ORR and DOR vs TPC across all TTP subgroups and in patients with primary and secondary endocrine resistance

Error bars represent 95% confidence intervals
*Endocrine resistance assessed by investigators per 5th ESO-ESMO advanced breast cancer guidelines. Primary endocrine resistance was defined as relapse in the first 2 years of adjuvant ET, or PD <6 mo of 1L ET for mBC. Secondary (acquired) endocrine resistance was defined as relapse after the first 2 years on adjuvant ET, or relapse within 12 mo of completing adjuvant ET, or PD >6 mo after initiating ET for mBC[1]
1L, first line; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ESO-ESMO, European School of Oncology-European Society for Medical Oncology; ET, endocrine therapy; mBC, metastatic breast cancer; mo, months; ORR, objective response rate; PD, progressive disease; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; TTP, time to progression
1. Cardoso F, et al. *Ann Oncol*. 2020;31:1623–1649

PFS2 in the overall ITT population and time-to-progression subgroups



Number at risk

T-DXd	436	431	396	365	322	268	176	115	78	43	23	11	4	1	0
TPC	430	399	365	311	244	183	109	69	48	26	12	6	2	0	0

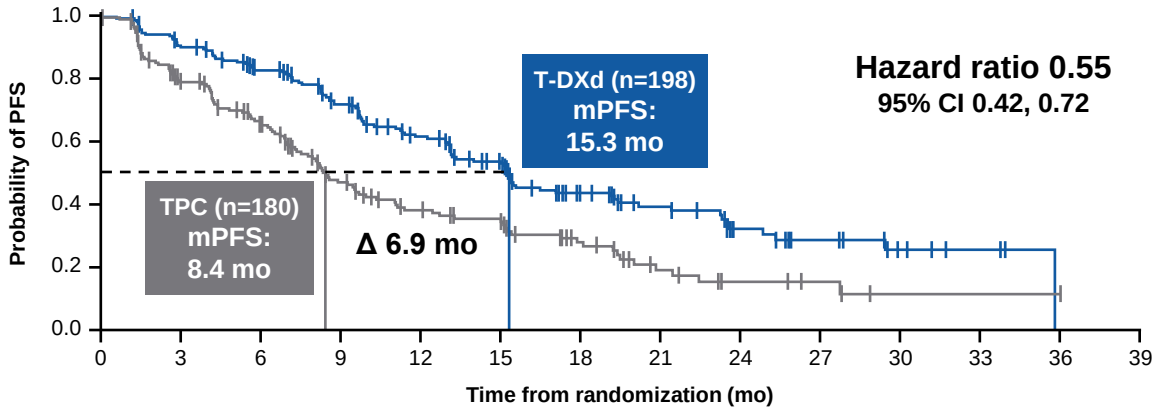
	<6-mo 1L TTP		6–12-mo 1L TTP		>12-mo 1L TTP	
	T-DXd (n=65)	TPC (n=59)	T-DXd (n=60)	TPC (n=52)	T-DXd (n=168)	TPC (n=166)
mPFS2, mo (95% CI)	18.9 (14.4, 24.0)	15.2 (10.9, 17.5)	17.1 (13.9, 31.8)	13.7 (10.3, 17.1)	20.0 (18.6, 25.3)	14.3 (12.6, 15.9)
PFS2 hazard ratio (95% CI)	0.73 (0.46, 1.14)†		0.59 (0.37, 0.94)†		0.57 (0.43, 0.75)†	

Delay in PFS2‡ was clinically meaningful in favor of T-DXd in the ITT population and TTP subgroups

*Of patients who received immediate post-discontinuation therapy (n=608), regimens included chemotherapy (66.7%), endocrine-based therapy (26.0%), ADC (7.8%), and targeted therapy alone (2.5%); †the hazard ratio and its CI was estimated from an unstratified Cox proportional hazards model; ‡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
ADC, antibody-drug conjugate; CI, confidence interval; ET, endocrine therapy; ITT, intent-to-treat; mo, months; (m)PFS2, (median) second progression-free survival / time from randomization to second progression or death;
T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; TTP, time to progression

PFS by measures of disease burden

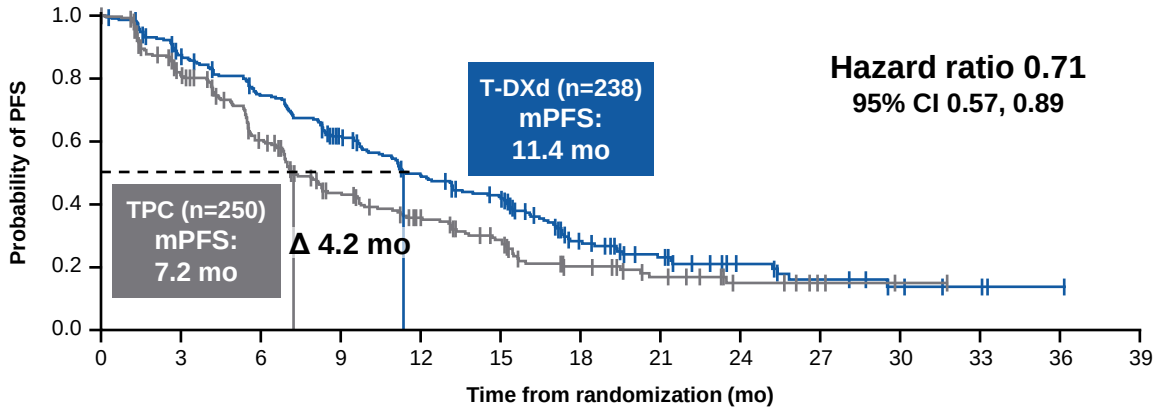
<3 local/metastatic sites at baseline



Number at risk

T-DXd	198	175	152	125	97	76	45	32	18	12	6	3	0	0
TPC	180	125	99	62	45	37	22	11	6	4	1	1	1	0

≥3 local/metastatic sites at baseline

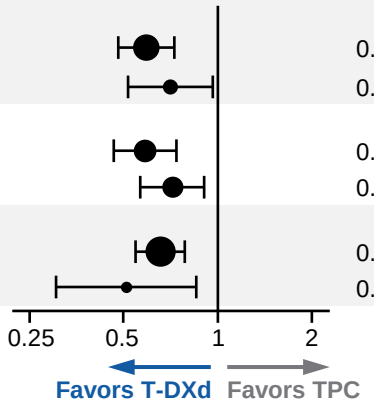


Number at risk

T-DXd	238	200	167	133	102	80	37	24	14	9	5	3	1	0
TPC	250	181	125	80	58	42	22	14	7	3	1	0	0	0

PFS benefit with T-DXd was observed regardless of disease burden, with notable efficacy in patients with lower disease burden

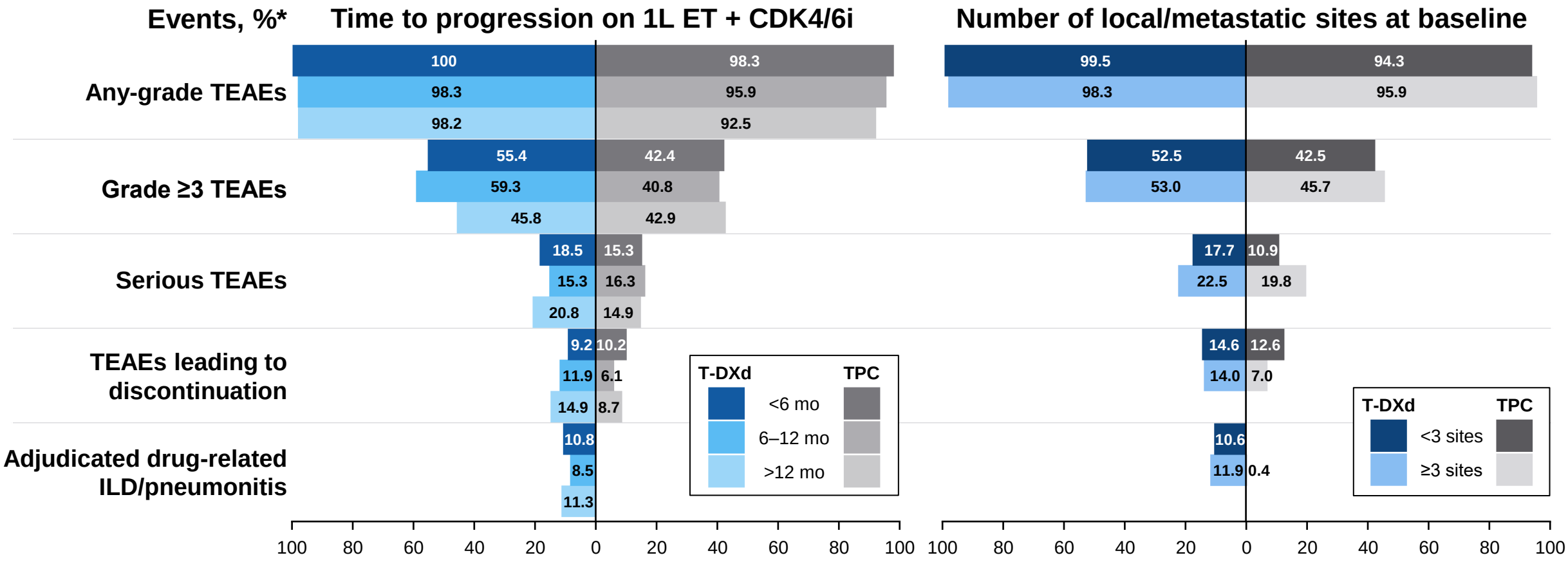
	mPFS, mo (95% CI)		Hazard ratio (95% CI)
	T-DXd	TPC	
Liver metastases			
Yes (n=579)	12.2 (10.4, 13.5)	7.0 (6.4, 8.1)	0.59 (0.48, 0.72)
No (n=287)	16.5 (13.2, 19.4)	11.3 (8.3, 15.2)	0.70 (0.51, 0.96)
Baseline tumor size*			
>Median (n=432)	12.0 (9.9, 15.2)	7.1 (6.5, 8.3)	0.57 (0.45, 0.72)
≤Median (n=434)	15.0 (13.1, 16.1)	9.7 (7.5, 13.2)	0.71 (0.55, 0.90)
Visceral disease			
Yes (n=740)	13.1 (11.1, 15.1)	7.9 (6.9, 8.5)	0.65 (0.55, 0.78)
No (n=126)	23.3 (13.1, NE)	11.3 (6.9, 15.7)	0.51 (0.30, 0.85)



*Median baseline tumor size in the ITT population (per BICR) was 48.6 mm, considering '0' as baseline tumor size for patients without target lesion at baseline

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; ET, endocrine therapy; HR, hazard ratio; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; NE, not evaluable; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

Safety in time-to-progression and disease burden subgroups



Safety profiles for T-DXd and TPC in time-to-progression and disease burden subgroups were in line with the overall safety population†

*Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent cancer therapy (whichever occurs first). Includes ILD/pneumonitis with an onset date or worsening on or after the date of first dose; †overall safety population (T-DXd vs TPC): any TEAEs, 98.8% vs 95.2%; Grade ≥3 TEAEs, 52.8% vs 44.4%; serious TEAEs, 20.3% vs 16.1%; TEAEs leading to discontinuation, 14.3% vs 9.4%; adjudicated drug-related ILD/pneumonitis, 11.3% vs 0.2%[1,2]

1L, first line; AE, adverse event; ET, endocrine therapy; ILD, interstitial lung disease; mo, months; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, physician's choice of chemotherapy; TTP, time to progression

1. Curigliano G, et al. Oral presentation at ASCO 2024 (Abstract LBA1000); 2. Bardia A, et al. *N Engl J Med*. 2024;391:2110–2122

Conclusions

- T-DXd demonstrated a clinically meaningful efficacy benefit vs TPC regardless of TTP on 1L ET + CDK4/6i (**mPFS 12.9–14.0 mo with T-DXd**)
  - This included patients with rapid (<6-mo) progression on 1L ET + CDK4/6i
- Efficacy outcomes were consistent in patients with primary and secondary endocrine resistance (**mPFS 12.4–13.2 mo with T-DXd**)
- PFS2 favored T-DXd over TPC in the overall population (**mPFS2 20.3 mo with T-DXd**) and in all TTP subgroups (**mPFS2 17.1–20.0 mo with T-DXd**), indicating a sustained benefit with T-DXd beyond initial disease progression
- T-DXd also demonstrated efficacy regardless of disease burden, with notable efficacy in patients with low disease burden (**mPFS 15.0–23.3 mo with T-DXd**)
- Safety profiles in subgroups were consistent with the overall safety population

T-DXd is an effective treatment option in a wide range of patients with HR+, HER2-low/-ultralow mBC following ≥1 endocrine-based therapy

Scan below to access a copy of the slides

This study was sponsored and designed by AstraZeneca, in collaboration with Daiichi Sankyo. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201)
Thank you to the patients and their families for their participation and the study site staff for their contributions
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1L, first line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; mBC, metastatic breast cancer; mo, months; mPFS, median progression-free survival; (m)PFS2, (median) second progression-free survival / time from randomization to second progression or death; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; TTP, time to progression

Additional data

Baseline characteristics and prior therapies by TTP on 1L ET + CDK4/6i

	<6-mo 1L TTP*		6–12-mo 1L TTP*		>12-mo 1L TTP*	
	T-DXd (n=65)	TPC (n=59)	T-DXd (n=60)	TPC (n=52)	T-DXd (n=168)	TPC (n=166)
De-novo disease at diagnosis, n (%)	12 (18.5)	13 (22.0)	25 (41.7)	22 (42.3)	61 (36.3)	64 (38.6)
Bone-only disease at baseline, n (%)	1 (1.5)	0	1 (1.7)	1 (1.9)	6 (3.6)	11 (6.6)
Liver metastases at baseline, n (%)	51 (78.5)	41 (69.5)	43 (71.7)	35 (67.3)	124 (73.8)	111 (66.9)
Investigator-assessed endocrine resistance at baseline, n (%)†						
Primary	59 (90.8)	55 (93.2)	12 (20.0)	15 (28.8)	15 (8.9)	14 (8.4)
Secondary	6 (9.2)	4 (6.8)	48 (80.0)	37 (71.2)	153 (91.1)	151 (91.0)
ECOG PS at screening, n (%)‡						
0	36 (55.4)	44 (74.6)	28 (46.7)	31 (59.6)	104 (61.9)	101 (60.8)
1	28 (43.1)	15 (25.4)	30 (50.0)	20 (38.5)	61 (36.3)	58 (34.9)
Number of prior lines of ET, metastatic setting						
1	33 (50.8)	40 (67.8)	11 (18.3)	15 (28.8)	12 (7.1)	12 (7.2)
2	26 (40.0)	18 (30.5)	42 (70.0)	35 (67.3)	132 (78.6)	128 (77.1)
≥3	6 (9.2)	1 (1.7)	7 (11.7)	2 (3.8)	24 (14.3)	26 (15.7)
Number of prior lines of ET + CDK4/6i, metastatic setting						
1	54 (83.1)	56 (94.9)	51 (85.0)	52 (100.0)	154 (91.7)	150 (90.4)
2	11 (16.9)	3 (5.1)	9 (15.0)	0	14 (8.3)	16 (9.6)
Prior therapies, adjuvant/neoadjuvant setting, n (%)§						
ET	51 (78.5)	41 (69.5)	29 (48.3)	29 (55.8)	92 (54.8)	86 (51.8)
Cytotoxic chemotherapy	44 (67.7)	35 (59.3)	25 (41.7)	27 (51.9)	73 (43.5)	78 (47.0)

*TTP analysis included 570 patients with PD on prior 1L ET + CDK4/6i (65.8% of the ITT population); †endocrine resistance assessed by investigators per 5th ESO-ESMO advanced breast cancer guidelines. Primary endocrine resistance was defined as relapse in the first 2 years of adjuvant ET, or PD <6 mo of 1L ET for mBC. Secondary (acquired) endocrine resistance was defined as relapse after the first 2 years on adjuvant ET, or relapse within 12 mo of completing adjuvant ET, or PD >6 mo after initiating ET for mBC;[1] ‡ECOG PS scores were missing for n=1 patient with <6-mo TTP, n=3 patients with 6–12-mo TTP, and n=9 patients with >12-mo TTP; n=1 patient with >12-mo TTP treated with T-DXd had an ECOG PS score of 2; §therapies reported are not mutually exclusive

1L, first line; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ESO-ESMO, European School of Oncology-European Society for Medical Oncology; ET, endocrine therapy; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; PD, progression of disease; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy; TTP, time to progression

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