A DESTINY-Breast09 analysis of treatment duration and clinical outcomes by best response to trastuzumab deruxtecan (T-DXd) + pertuzumab (P)

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Key takeaway points/conclusions

DESTINY-Breast09

1

In DESTINY-Breast09, achieving a CR or deep PR (≥80% tumor reduction) was associated with improved long-term outcomes in the T-DXd + P arm

2

Over half of the patients (~53%) achieved a CR or deep PR with T-DXd + P

Achieving CR and deep PR yielded comparable improved PFS benefit

3

Responses deepened over time, with 80% of patients achieving maximal tumor reduction by 24 months

Patients who achieved CR and deep PR had the longest treatment duration

CR, complete response; P, pertuzumab; PFS, progression-free survival; PR, partial response; T-DXd, trastuzumab deruxtecan.

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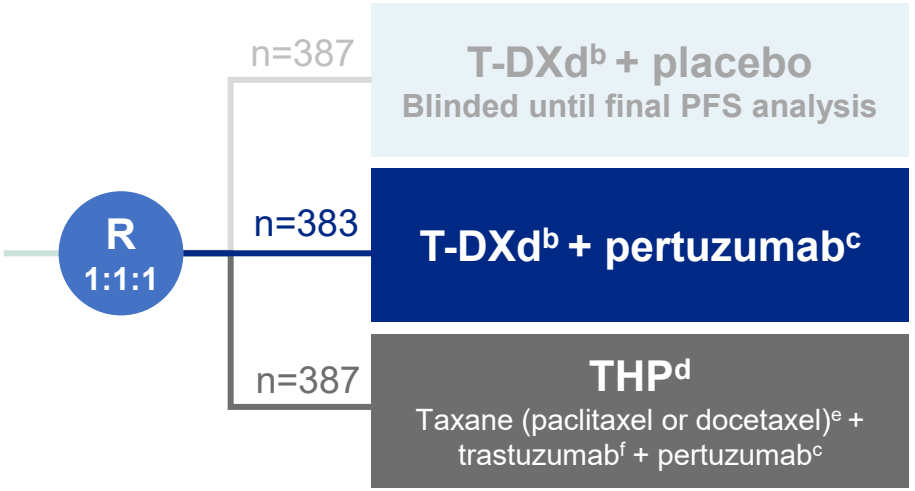
DESTINY-Breast09 study design
Randomized, multicenter, phase 3 study (NCT04784715)

Eligibility criteria

- HER2+ a/mBC
- **Asymptomatic/inactive** brain metastases allowed
- **DFI >6 mo** from last chemotherapy or HER2-targeted therapy in neoadjuvant/adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic treatment for mBC**[a]

Stratification factors

- De novo vs recurrent mBC
- HR+ or HR−
- *PIK3CA*m (detected vs non-detected)



Primary endpoints

- PFS (BICR)

Key secondary endpoint

- OS

Other secondary endpoints

- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety/tolerability

At the prespecified interim analysis, T-DXd + P met its primary endpoint (DCO: Feb 26, 2025; presented at ASCO 2025)[1,2]:

Efficacy

- **Median PFS:** 40.7 vs 26.9 mo with T-DXd + P vs THP, respectively (*P*<0.00001)[1g]
- **Confirmed ORR:** 85.1%[h] vs 78.6%[i] with T-DXd + P vs THP, respectively[1]
- **CRs nearly doubled** in the T-DXd + P vs THP arm (15.1% vs 8.5%, respectively)[1]

Safety

T-DXd + P safety data were **consistent** with the **known profiles** of individual treatments

The aim of this exploratory analysis was to evaluate the **association between depth of response to T-DXd + P treatment and long-term clinical benefit**

[a]HER2-targeted therapy or chemotherapy. [b]5.4 mg/kg Q3W. [c]840 mg loading dose, then 420 mg Q3W. [d]Open label for THP arm. Double-blinded for pertuzumab in experimental arms. [e]Paclitaxel 80 mg/m² QW or 175 mg/m² Q3W, or docetaxel 75 mg/m² Q3W for ≤6 cycles or intolerable toxicity. [f]8 mg/kg loading dose, then 6 mg/kg Q3W. [g]Hazard ratio, 0.56 (95% CI, 0.44, 0.71). [h]95% CI: 81.2, 88.5. [i]95% CI: 74.1, 82.5.
a/mBC, advanced/metastatic breast cancer; BICR, blinded independent central review; CI, confidence interval; DCO, data cutoff; DFI, disease-free interval; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; HR+/−, hormone receptor–positive/–negative; INV, investigator; mo, months; OS, overall survival; ORR, objective response rate; PFS2, second progression-free survival; *PIK3CA*m, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutation; Q3W, every 3 weeks; QW, once every week; R, randomization; THP, taxane + trastuzumab + pertuzumab. NCT04784715. Available from: https://clinicaltrials.gov/study/NCT04784715 (Accessed March 13, 2026).
1. Tolaney SM, et al. *J Clin Oncol.* 2025;43(17 Suppl):LBA 1008. 2. Tolaney SM, et al. *N Engl J Med.* 2026;394:551–562.

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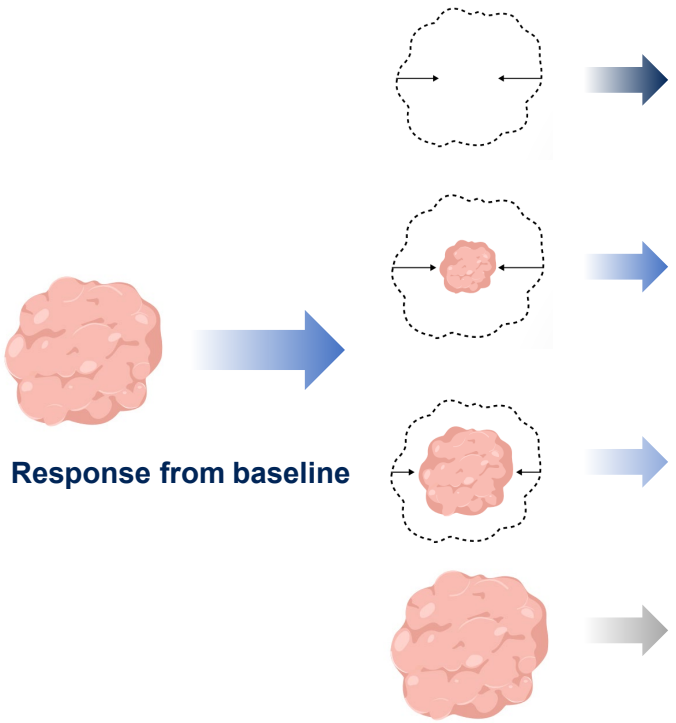
Exploratory analysis of response subgroups



CR
Per RECIST v1.1

Deep PR (≥80%)
PR with ≥80% to <100% reduction in TL sum[a]

PR (<80%)
Remaining patients with confirmed PR after excluding patients with **deep PR** (i.e. PR with ≥30% to <80% reduction in TL sum)[1]

SD/PD
Per RECIST v1.1

Endpoints evaluated in DESTINY-Breast09 response subgroups[b]:

- Time to best response
- Duration of response
- Progression-free survival
- Safety (including TEAEs and adjudicated drug-related ILD/pneumonitis)

Analyses were not pre-defined to allow comparisons between the T-DXd + P and THP arms

[a]PR with ≥80% to <100% reduction in TL sum and CR or non-CR/non-PD in non-TLs, or CR in TL and non-CR/non-PD in non-TLs. [b]Data cut-off date: February 26, 2025. Endpoints were analyzed by the best confirmed response by BICR of CT or MRI every 6 weeks from randomization for 48 weeks and then every 9 weeks until disease progression.
CT, computed tomography; ILD, interstitial lung disease; MRI, magnetic resonance imaging; PD, progressive disease; RECIST, Response Evaluation in Solid Tumors; SD, stable disease; TEAE, treatment-emergent adverse event; TL, target lesion.
1. Hamilton E, et al. Poster presented at the European Society for Medical Oncology Breast Cancer (ESMO BC) Annual Meeting; May 14-17, 2026; Munich, Germany.

Patient disposition: T-DXd + P arm

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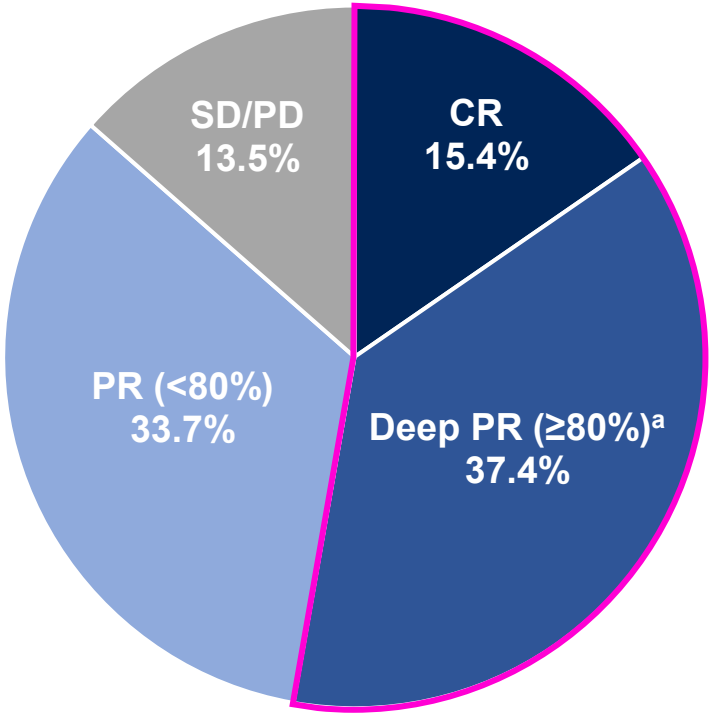
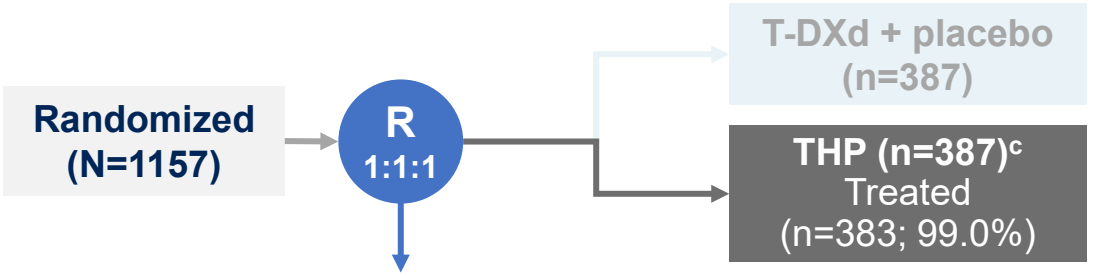
Response Categories (n=377)





T-DXd + P (n=383) Full analysis set (n=377; 98.4%)[b]	CR (n=58)	Deep PR[a] (n=141)	PR (<80%) (n=127)	SD/PD (n=51)[d]
Subjects with ongoing T-DXd at DCO, n (%)	32 (55.2)	67 (47.5)	47 (37.0)	6 (12.0)
Discontinued T-DXd, n (%)	26 (44.8)	74 (52.5)	80 (63.0)	44 (88.0)
Reasons for T-DXd discontinuation, n (%)				
PD	5 (8.6)	23 (16.3)	33 (26.0)	19 (38.0)
AE	17 (29.3)	26 (18.4)	28 (22.0)	7 (14.0)
Patient decision	4 (6.9)	15 (12.1)	15 (10.4)	8 (16.0)
Other	0	8 (5.7)[e]	6 (4.7)	10 (20.0)
Death	0	2 (1.4)	4 (3.1)	8 (16.0)
Transitioned to trastuzumab, n (%)	8 (13.8)	11 (7.8)	10 (6.9)	5 (10.0)

Over half of patients (~53%) achieved CR or deep PR

[a]PR with ≥80% to <100% reduction in TL sum and CR or non-CR/non-PD in non-TLs, or CR in TL and non-CR/non-PD in non-TLs. [b]6 patients with status NE were excluded from the analyses as the best response cannot be calculated. [c]Data for the THP arm are available at the QR code shared at the end of the presentation. [d]1 patient did not start treatment. [e]Includes 1 patient with a protocol violation.
AE, adverse event; NE, not evaluable.

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Patient demographic and key baseline characteristics: T-DXd + P arm

	CR (n=58)	Deep PR[a] (n=141)	PR (<80%) (n=127)	SD/PD (n=51)
Age, median (range), years	53.5 (29–81)	54.0 (27–79)	54.0 (29–81)	52.0 (27–85)
De novo disease at diagnosis, n (%)	33 (56.9)	79 (56.0)	69 (54.3)	18 (35.3)
HR status, n (%)				
Positive[b]	30 (51.7)	65 (46.1)	73 (57.5)	35 (68.6)
Negative	28 (48.3)	76 (53.9)	54 (42.5)	16 (31.4)
***PIK3CA* mutations detected, n (%)**	17 (29.3)	38 (27.0)	39 (30.7)	20 (39.2)
Brain metastases, n (%)[c]	2 (3.4)	12 (8.5)	6 (4.7)	4 (7.8)
Visceral metastases, n (%)	38 (65.5)	108 (76.6)	96 (75.6)	35 (68.6)
Time (years) from initial diagnosis to randomization, n (%)				
<2	34 (58.6)	83 (58.9)	75 (59.1)	21 (41.2)
2–5	16 (27.6)	38 (27.0)	32 (25.2)	16 (31.4)
>5	6 (10.3)	14 (9.9)	17 (13.4)	8 (15.7)
Disease-free interval[d], days				
Median (range)	595 (14–8410)	640 (25–7555)	397 (13–7894)	330 (19–4267)

Patient baseline characteristics were comparable across response subgroups

Note: Data for the THP arm are available at the QR code shared at the end of the presentation.
[a]PR with ≥80% to <100% reduction in TL sum and CR or non-CR/non-PD in non-TLs, or CR in TL and non-CR/non-PD in non-TLs. [b]Defined as estrogen receptor-positive and/or progesterone receptor-positive (≥1%). [c]Participants were eligible if they had brain metastases that were clinically inactive or treated/asymptomatic.
[d]Time from completion of previous anticancer therapy to randomization.

Progression-free survival: T-DXd + P arm

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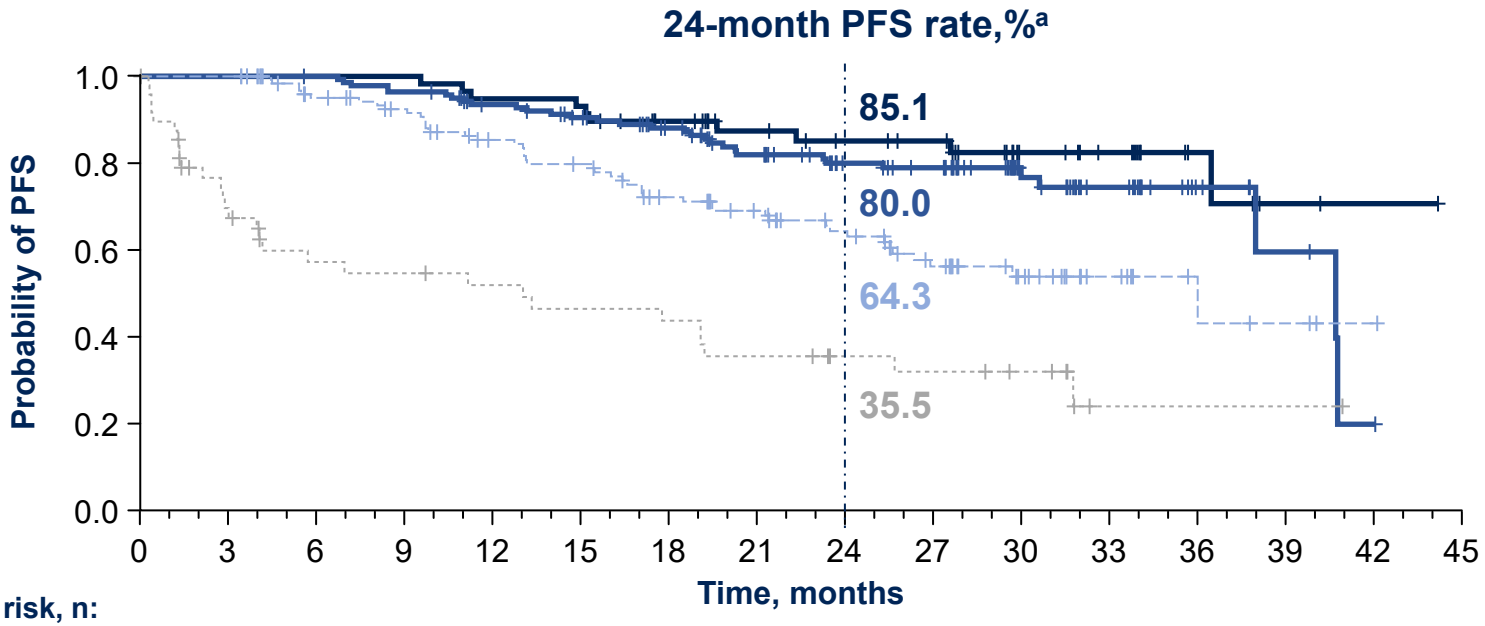

Patients at risk, n:

CR	58	58	58	58	55	54	47	39	35	33	21	16	7	2	1	0
Deep PR[b]	141	141	140	135	125	117	105	91	77	72	34	22	8	4	1	0
PR (<80%)	127	127	113	105	92	85	72	63	52	38	20	10	5	3	1	0
SD/PD	51	30	22	21	19	17	16	13	10	9	7	1	1	1	0	0

CR – Deep PR =

Δ 5.1%

Deep PR – PR (<80%) =

Δ 15.7%

Achieving CR and deep PR was associated with similar durable PFS outcomes

[a]95% CIs for 24-mo PFS rates: CR: 72.2, 92.3; deep PR: 71.7, 86.1; PR (<80%): 54.3, 72.8; SD/PD: 21.1, 50.2. [b]PR with ≥80% to <100% reduction in TL sum and CR or non-CR/non-PD in non-TLs, or CR in TL and non-CR/non-PD in non-TLs.

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Response characteristics: T-DXd + P arm

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	CR (n=58)	Deep PR[a] (n=141)	PR (<80%) (n=127)	SD/PD (n=51)
Time to best response (median, mo) [95% CI]	8.4 [5.6, 11.1]	9.6 [6.8, 11.0]	1.5 [1.4, 2.0]	NA
Duration of best response (median, mo) [95% CI]	NC [35.1, NC]	39.2 [35.3, NC]	34.8 [22.8, NC]	NA
Patients remaining in best response, % [95% CI]				
12 mo	94.8 [84.8, 98.3]	91.3 [85.1, 95.0]	78.9 [70.1, 85.3]	NA
24 mo	85.0 [72.1, 92.3]	78.9 [70.4, 85.2]	60.4 [50.0, 69.3]	NA
Total treatment duration, (median, mo) [range][b]	28.0 [4.8–44.5]	25.4 [3.4–42.7]	20.6 [2.8–41.8]	4.4 [0.3–37.2]
PFS at 24 mo, % [95% CI]	85.1 [72.2, 92.3]	80.0 [71.7, 86.1]	64.3 [54.3, 72.8]	35.5 [21.1, 50.2]

80% of patients (ITT) achieved **maximal tumor reduction** by **24 months**

Patients who achieved CR and deep PR had the longest treatment duration, with responses deepening over time

[a]PR with ≥80% to <100% reduction in TL sum and CR or non-CR/non-PD in non-TLs, or CR in TL and non-CR/non-PD in non-TLs. [b]Per protocol, a small proportion of patients in each group transitioned to trastuzumab (CR, 8 [13.8%]; deep PR, 11 [7.8%]; PR (<80%), 10 [6.9%]; SD/PD, 5 [10.0%]).
ITT, intention to treat; NA, not applicable; NC, not calculable.

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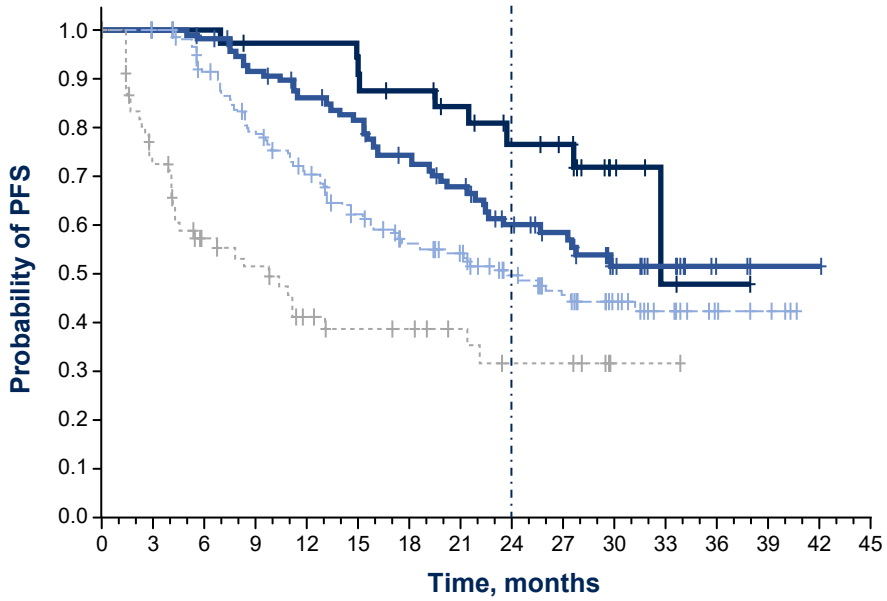
Responder analysis: THP arm[a]

	CR (n=33)	Deep PR[b] (n=110)	PR (<80%) (n=161)	SD/PD (n=68)
Time to best response (median, mo) [95% CI]	5.6 [2.8, 9.8]	8.2 [6.8, 9.6]	1.5 [1.4, 1.5]	NA
Duration of best response (median, mo) [95% CI]	31.3 [31.3, NC]	NC [22.3, NC]	20.1 [13.1, 30.1]	NA
Patients remaining in best response, % [95% CI]				
12 mo	93.7 [77.2, 98.4]	83.8 [75.2, 89.6]	61.9 [53.6, 69.2]	NA
24 mo	76.4 [56.5, 88.1]	60.4 [49.9, 69.4]	46.5 [37.7, 54.9]	NA
Total treatment duration (median, mo), range[c]	28.1 (7.6–38.2)	20.2 (2.7–40.8)	17.9 (2.9–41.7)	5.9 (1.4–35.2)
PFS at 24 mo, % [95% CI]	76.7 [56.9, 88.2]	60.7 [50.3, 69.6]	48.5 [39.8, 56.6]	31.7 [18.6, 45.5]



In the THP arm, achieving deep PR was not associated with similar outcomes to achieving CR

[a]Median duration of follow-up (range, mo): CR: 29.5 (20.8–38.9); deep PR: 30.5 (11.3–43.2); PR (<80%): 29.2 (5.5–44.7); SD/PD: 20.1 (2.4–40.9). [b]PR with ≥80% to <100% reduction in TL sum and CR or non-CR/non-PD in non-TLs, or CR in TL and non-CR/non-PD in non-TLs. [c]Includes both the induction and maintenance phases.

Overall safety summary: T-DXd + P arm[a]

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	CR (n=58)	Deep PR[b] (n=142)	PR (<80%) (n=128)	SD/PD (n=49)
Possibly treatment-related TEAEs[c], n (%)	37 (63.8)	77 (54.2)	68 (53.1)	25 (51.0)
Grade ≥3				
EAIRs of drug-related grade ≥3 AEs, per patient-year	0.30	0.28	0.32	0.57
Serious TEAEs, n (%)	16 (27.6)	35 (24.6)	36 (28.1)	13 (26.5)
TEAEs associated with any treatment discontinuation, n (%)	18 (31.0)[d]	26 (18.3)	27 (21.1)	7 (14.3)
EAIRs of TEAEs associated with any study drug discontinuation, per patient-year	0.14	0.10	0.13	0.16
TEAEs associated with any dose interruptions, n (%)	45 (77.6)	106 (74.6)	85 (66.4)	24 (49.0)
TEAEs associated with any dose reductions, n (%)	33 (56.9)	72 (50.7)	52 (40.6)	16 (32.7)
Possibly treatment-related TEAEs associated with an outcome of death, n (%)	0	1 (0.7)	1 (0.8)	3 (6.1)
Adjudicated drug-related ILD/pneumonitis, n (%)	7 (12.1)	22 (15.5)	10 (7.8)	6 (12.2)
Grade ≥3	0	0	0	2 (4.1)
Left ventricular dysfunction, n (%)	8 (13.8)	15 (12.0)	14 (9.7)	4 (8.2)
Grade ≥3	2 (3.4)	4 (2.8)	1 (0.8)	1 (2.0)

EAIRs for drug-related grade ≥3 AEs were similar across different responder subgroups, with no new safety signals identified

Note: Data for the THP arm are available at the QR code shared at the end of the presentation. [a]Total treatment duration (median, mo): CR, 28.0; Deep PR, 25.4; PR (<80%), 20.6; SD/PD, 4.4. [b]PR with ≥80% to <100% reduction in TL sum and CR or non-CR/non-PD in non-TLs, or CR in TL and non-CR/non-PD in non-TLs. [c]Investigator assessed. [d]17/18 were T-DXd discontinuations.
EAIR, exposure-adjusted incidence rate.

Conclusions

- In **DESTINY-Breast09**, achieving a CR or deep PR (≥80% tumor reduction) was associated with improved long-term outcomes in the T-DXd + P arm
- **Over half (~53%) of patients** achieved deep and durable responses with **T-DXd + P**
  - Achieving CR and deep PR[a] yielded comparable improved benefit (24-month PFS rates: 85% and 80%)
  - Patients with CR and deep PR had the longest median treatment durations (28 and 25 months)
- **Responses deepened over time**, with 80% of patients achieving maximal tumor reduction by 24 months, highlighting the importance of maintaining first-line therapy to sustain clinical benefit
- EAIRs for drug-related grade ≥3 AEs were similar across different responder subgroups, with no new safety signals identified

These data reinforce the importance of achieving deep and durable responses to improve long-term clinical outcomes in first-line HER2+ mBC

[a]PR with ≥80% to <100% reduction in TL sum and CR or non-CR/non-PD in non-TLs, or CR in TL and non-CR/non-PD in non-TLs.

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Supplementary content is available:
Results from the THP arm
of DESTINY-Breast09

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