2024 ASCO® ANNUAL MEETING

DESTINY BREAST06

Trastuzumab deruxtecan vs physician's choice of chemotherapy in patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–low or HER2-ultralow metastatic breast cancer with prior endocrine therapy: primary results from DESTINY-Breast06

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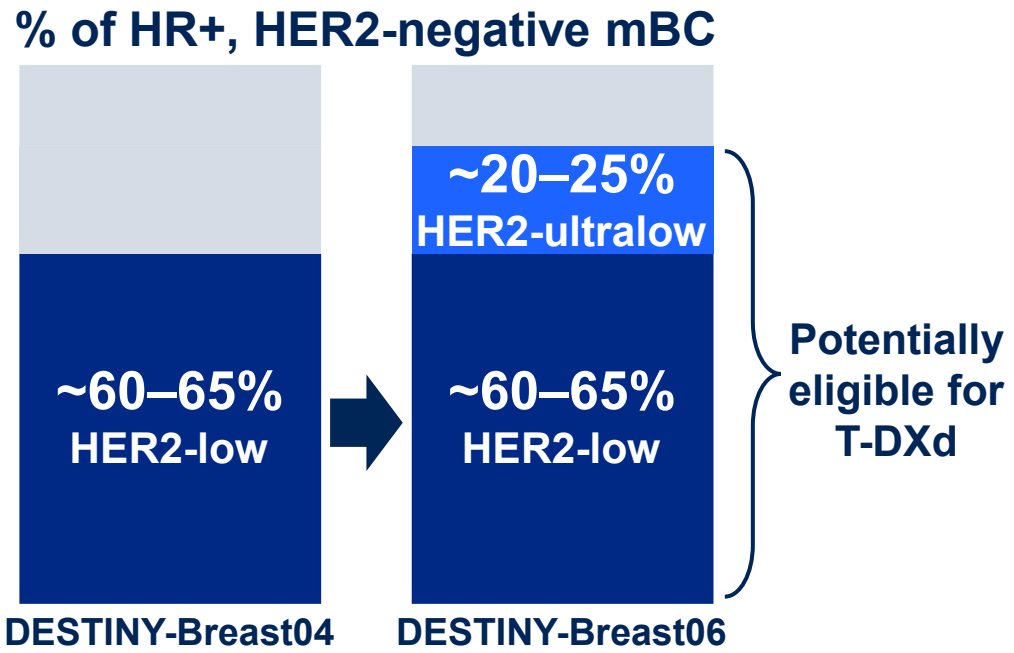
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On behalf of the DESTINY-Breast06 investigators

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DESTINY-Breast06: key takeaways



- T-DXd demonstrated efficacy in **HER2-low mBC** in an **earlier line of treatment** to DESTINY-Breast04
- Including HER2-ultralow, the proportion of patients who could benefit from T-DXd is **~85% of HR+, HER2-negative mBC** after DESTINY-Breast06

In DESTINY-Breast06, T-DXd demonstrated a statistically significant and clinically meaningful PFS benefit vs TPC (chemotherapy) in HR+, HER2-low mBC after ≥1 endocrine-based therapy, with consistent results in HER2-ultralow mBC

HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; mBC, metastatic breast cancer; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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Unmet treatment need in HR+, HER2-negative mBC

Current treatment landscape and outcomes: mPFS*

1L	ET + CDK4/6i	*No prior CDK4/6i*	24.8–28.2 mo[1–3]
2L+	ET + targeted therapies	*Prior CDK4/6i*	5.5 mo[4]
	ET monotherapy	*Prior CDK4/6i*	1.9–2.6 mo[4,5]
3L+	Single-agent CT	*Mostly CT naïve (mBC)*	6.2–7.1 mo[6–8]
	T-DXd (HER2-low)	*Prior ET and CT*	10.1 mo[9]

*Based on data from Phase 3 registrational studies only

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CT, chemotherapy; 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; T-DXd, trastuzumab deruxtecan

1. Finn RS, et al. *N Engl J Med.* 2016;375:1925–1936; 2. Hortobagyi GN, et al. *Ann Oncol.* 2018;29:1541–1547; 3. Johnston S, et al. *NPJ Breast Cancer.* 2019;5:5; 4. Turner NC, et al. *N Engl J Med.* 2023;388:2058–2070 (Supplementary Appendix); 5. Bidard FC, et al. *J Clin Oncol.* 2022;40:3246–3256; 6. O'Shaughnessy J, et al. *JAMA Netw Open.* 2021;4:e214103; 7. O'Shaughnessy J, et al. *Cancer Res.* 2021;81(Suppl. 4):Abstract GS4-01; 8. Robert NJ, et al. *J Clin Oncol.* 2011;29:1252–1260; 9. Modi S, et al. *N Engl J Med.* 2022;387:9–20

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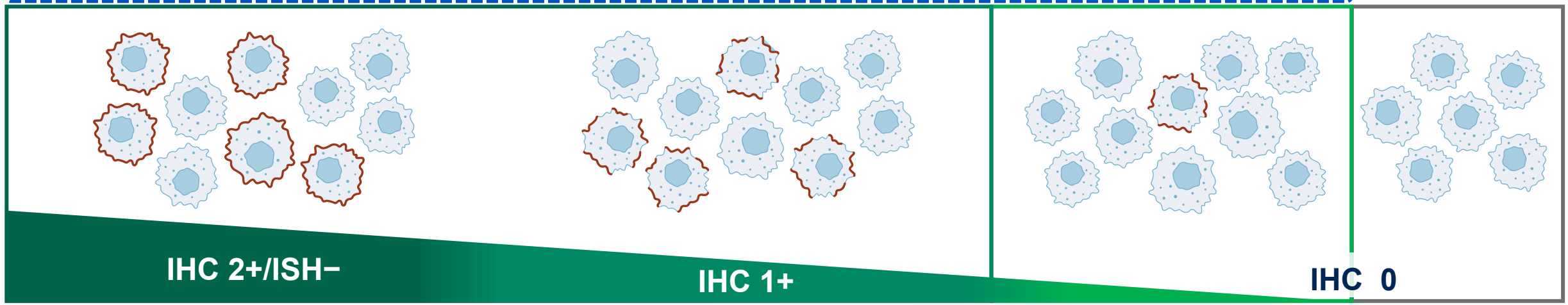
Targeting ‘low’ and ‘ultralow’ HER2-expressing tumors in mBC

HER2 IHC categories within HR+, HER2-negative (HER2−) mBC (per ASCO/CAP[1])

DESTINY-Breast06 patient population: ~85% of HR+, HER2− mBC

HER2-low ~60–65%[2,3]

HER2-ultralow ~20–25%[2–4]



IHC 2+/ISH−	IHC 1+	IHC 0	
Weak-to-moderate complete membrane staining in >10% tumor cells	Faint, incomplete membrane staining in >10% tumor cells	**Faint, incomplete membrane staining in ≤10% tumor cells**	Absent / no observable membrane staining

ASCO/CAP, American Society of Clinical Oncology / College of American Pathologists; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

Images adapted from Venetis K, et al. *Front Mol Biosci.* 2022;9:834651. CC BY 4.0 license available from: https://creativecommons.org/licenses/by/4.0/

1. Wolff AC, et al. *J Clin Oncol.* 2023;41:3867–3872; 2. Denkert C, et al. *Lancet Oncol.* 2021;22:1151–1161; 3. Chen Z, et al. *Breast Cancer Res Treat.* 2023;202:313–323; 4. Mehta S, et al. *J Clin Oncol.* 2024;42(Suppl. 16):Abstract e13156

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Study design

DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

PATIENT POPULATION

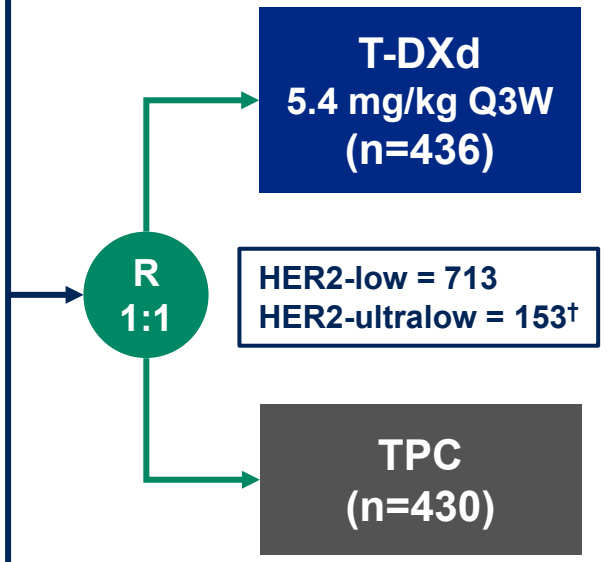
- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)



ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

*Study enrollment was based on central HER2 testing. HER2 status was determined based on the most recent evaluable HER2 IHC sample prior to randomization. HER2-ultralow was defined as faint, partial membrane staining in ≤10% of tumor cells (also known as IHC >0<1+); †HER2-ultralow status as determined per IRT data (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 as determined per central laboratory testing data); ‡to be presented separately
BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; INV, investigator assessed; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice
NCT04494425. Updated. April 12, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed May 13, 2024)

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Statistical analysis

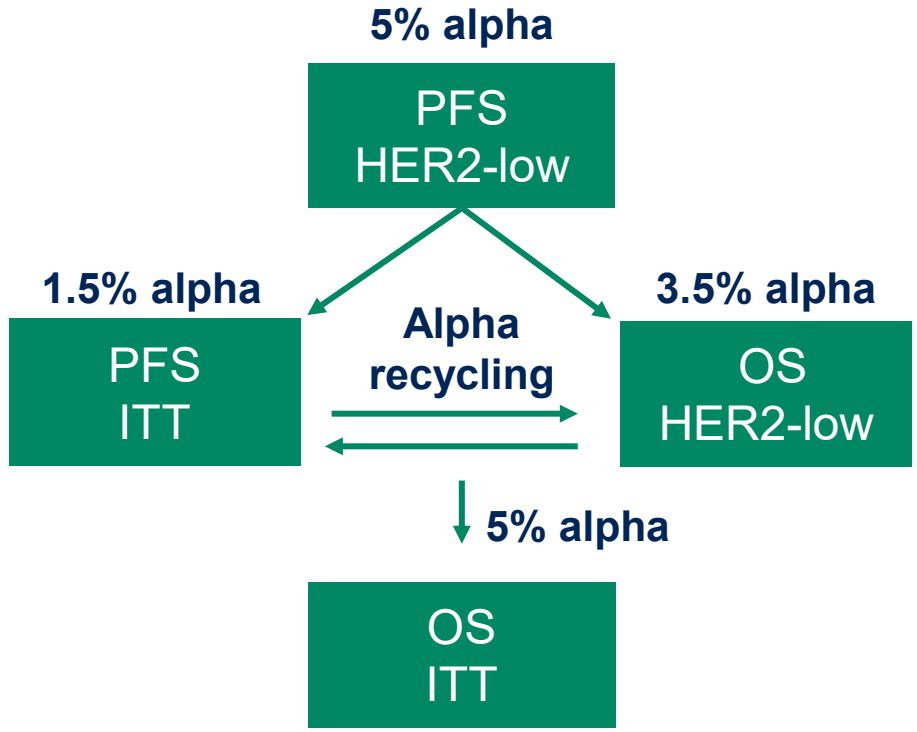
PFS primary analysis by BICR (HER2-low)
(planned after approximately 456 events)

- At DCO (March 18, 2024), there were 457 BICR-assessed PFS events in HER2-low
  - 540 events occurred in the ITT (HER2-low + -ultralow)

First interim OS analysis
(at time of primary analysis)

- At DCO, there were 282 events in the HER2-low and 335 events in the ITT (HER2-low + -ultralow) **(maturity: ~40% of total N)**
- Second interim and final OS analyses will be performed in HER2-low at ~56% and ~74% maturity, respectively

Multiple testing procedure*



*Updated significance levels were determined using a Lan-DeMets alpha-spending function with an O'Brien-Fleming boundary
BICR, blinded independent central review; DCO, data cutoff; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival

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Patient disposition

Screened (N=1349)

Randomized 1:1 (N=866)

T-DXd (n=436)
Treated (99.5%)

- Discontinued study treatment (79.5%)
  - PD (57.1%)
  - Adverse event (14.1%)
  - Patient decision (4.4%)
  - Other (3.9%)
    - Death (1.2%)

TPC (n=430)
Treated (97.0%)

- Discontinued study treatment (92.8%)
  - PD (70.0%)
  - Adverse event (9.4%)
  - Patient decision (8.2%)
  - Protocol non-compliance (0.2%)
  - Other (5.0%)
    - Death (1.0%)

	n (%)
Capecitabine	257 (59.8)
Nab-paclitaxel	105 (24.4)
Paclitaxel	68 (15.8)

At DCO, 119 patients (14.0%) remained on treatment: 89 (20.5%) T-DXd and 30 (7.2%) TPC
Median duration of follow up: 18.2 months (ITT)

DCO, data cutoff; ITT, intent-to-treat; PD, progressive disease; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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Patient demographics and key baseline characteristics

	HER2-low*		ITT (HER2-low and HER2-ultralow)		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Age, median (range), years	58.0 (28–87)	57.0 (32–83)	58.0 (28–87)	57.0 (32–83)	58.0 (33–85)	57.5 (34–82)
Female, n (%)	359 (100)	353 (99.7)	436 (100)	429 (99.8)	76 (100)	76 (100)
ECOG PS at screening, n (%)†						
0	207 (57.7)	218 (61.6)	252 (57.8)	257 (59.8)	44 (57.9)	39 (51.3)
1	148 (41.2)	128 (36.2)	178 (40.8)	163 (37.9)	30 (39.5)	35 (46.1)
HER2 status, n (%)‡						
IHC 0 with membrane staining (HER2-ultralow)	–	–	76 (17.4)	76 (17.7)	76 (100)	76 (100)
IHC 1+ (HER2-low)	238 (66.3)	234 (66.1)	239 (54.8)	234 (54.4)	–	–
IHC 2+/ISH− (HER2-low)	117 (32.6)	118 (33.3)	117 (26.8)	118 (27.4)	–	–
ER/PR status, n (%)§						
ER+/PR+	206 (57.4)	193 (54.5)	253 (58.0)	237 (55.1)	46 (60.5)	44 (57.9)
ER+/PR−	141 (39.3)	152 (42.9)	167 (38.3)	181 (42.1)	26 (34.2)	29 (38.2)
ER−/PR+	3 (0.8)	2 (0.6)	3 (0.7)	2 (0.5)	–	–
Primary endocrine resistance¶	105 (29.2)	116 (32.8)	128 (29.4)	140 (32.6)	23 (30.3)	24 (31.6)
De-novo disease at diagnosis, n (%)	111 (30.9)	104 (29.4)	133 (30.5)	132 (30.7)	22 (28.9)	28 (36.8)
Bone-only disease at baseline, n (%)	11 (3.1)	10 (2.8)	13 (3.0)	13 (3.0)	2 (2.6)	3 (3.9)
Visceral disease at baseline, n (%)	309 (86.1)	299 (84.5)	376 (86.2)	364 (84.7)	66 (86.8)	65 (85.5)
Liver metastases at baseline, n (%)	243 (67.7)	232 (65.5)	296 (67.9)	283 (65.8)	52 (68.4)	51 (67.1)

*HER2-low status defined at randomization per IRT data, and HER2-ultralow status defined per central laboratory testing data. With mis-stratification, the combined sample size of these two populations may not match the ITT total; †n=14 patients had missing ECOG PS status at baseline; ‡n=2 patients in the ITT (1 per treatment group) were found to have HER2 IHC 0 with absent membrane staining per central laboratory testing; §patients with ER−/PR− status were excluded from the study; however, n=1 patient with ER–/PR– status was randomized in error; ¶defined as relapse while on the first 2 years of adjuvant endocrine therapy, or progressive disease within the first 6 months of first-line endocrine therapy for metastatic breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; PR, progesterone receptor; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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Prior therapies

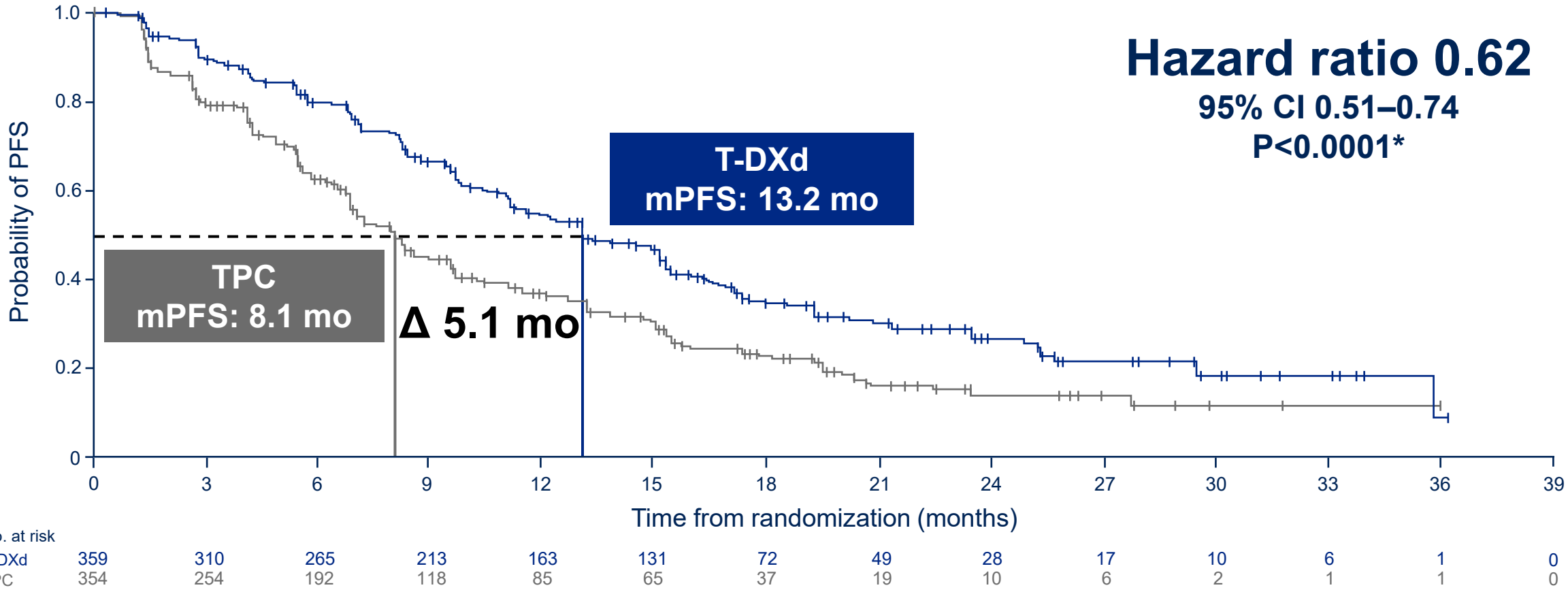
	HER2-low*		ITT (HER2-low and HER2-ultralow)		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
ET in the metastatic setting						
Lines of ET						
Number of lines, median (range)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)
Number of lines, n (%)						
1	54 (15.1)	67 (19.0)	65 (14.9)	82 (19.2)	11 (14.5)	15 (19.7)
≤6 months on first-line ET + CDK4/6i	33 (9.2)	33 (9.4)	37 (8.5)	40 (9.3)	4 (5.3)	7 (9.2)
2	242 (67.6)	236 (67.0)	295 (67.8)	288 (67.3)	52 (68.4)	52 (68.4)
≥3	62 (17.3)	49 (13.9)	75 (17.2)	58 (13.6)	13 (17.1)	9 (11.8)
Prior therapies, n (%)						
ET monotherapy	189 (52.6)	183 (51.7)	230 (52.8)	223 (51.9)	41 (53.9)	40 (52.6)
ET with CDK4/6i	318 (88.6)	316 (89.3)	388 (89.0)	385 (89.5)	69 (90.8)	69 (90.8)
ET with other targeted therapy†	120 (33.4)	105 (29.7)	143 (32.8)	127 (29.5)	22 (28.9)	22 (28.9)
Adjuvant/neoadjuvant setting‡						
Prior therapies, n (%)						
ET	227 (63.2)	218 (61.6)	275 (63.1)	256 (59.5)	48 (63.2)	38 (50.0)
Cytotoxic chemotherapy	192 (53.5)	196 (55.4)	228 (52.3)	234 (54.4)	36 (47.4)	38 (50.0)
Taxane	151 (42.1)	151 (42.7)	179 (41.1)	177 (41.2)	28 (36.8)	26 (34.2)
Anthracycline	167 (46.5)	173 (48.9)	197 (45.2)	206 (47.9)	30 (39.5)	33 (43.4)

*HER2-low status defined at randomization per IRT data, and HER2-ultralow status defined per central laboratory testing data; †other targeted therapies were mTORi (23.8%), PI3Ki (4.2%), or PARPi (0.9%) in the ITT; ‡approximately 30% of the patient population had de-novo metastatic disease and were not included in this category

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mTORi, mammalian target of rapamycin inhibitor; PARPi, poly-adenosine diphosphate ribose polymerase inhibitor; PI3Ki, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha inhibitor; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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PFS (BICR) in HER2-low: primary endpoint



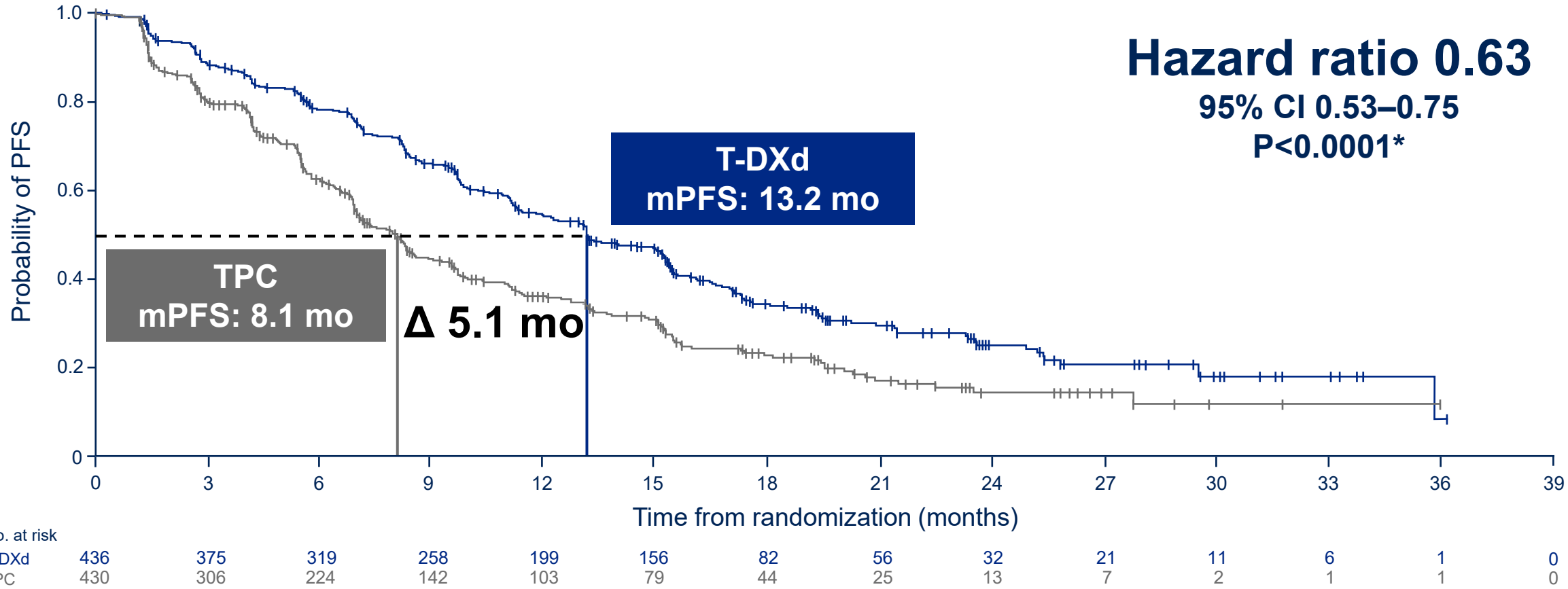
T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance

BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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PFS (BICR) in ITT: key secondary endpoint



T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in ITT

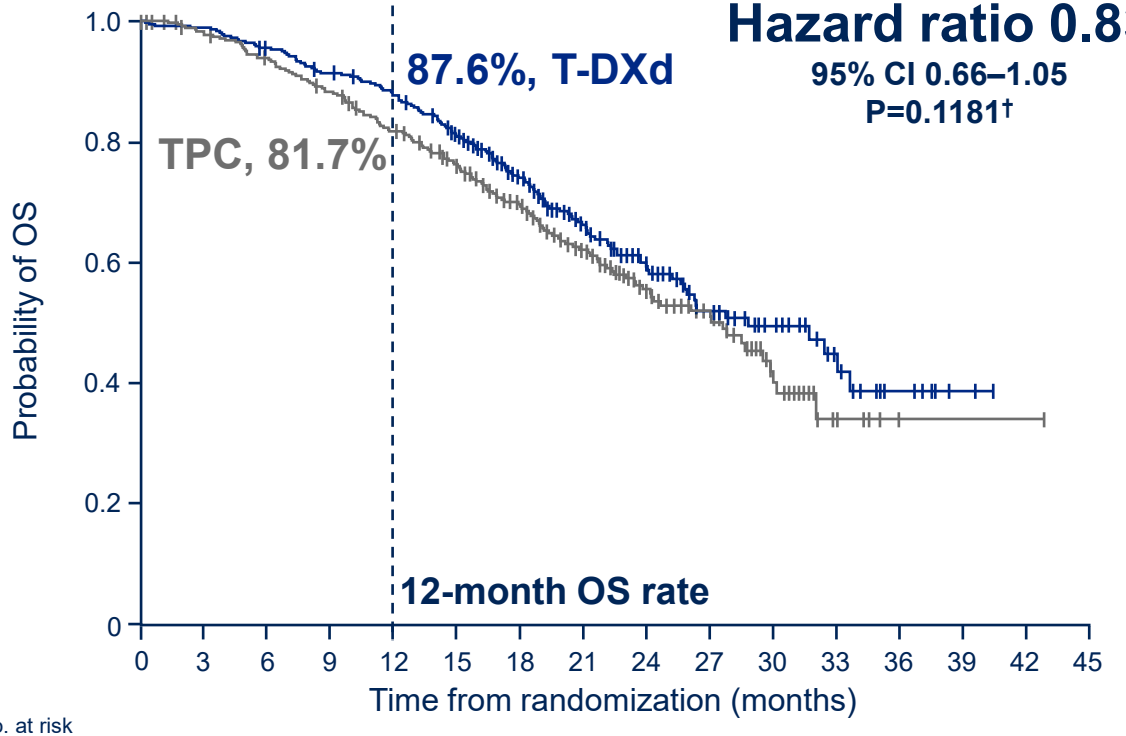
*P-value of <0.015 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; ITT, intent-to-treat; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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OS in HER2-low and ITT: key secondary endpoints (~40% maturity)

HER2-low*

n=713



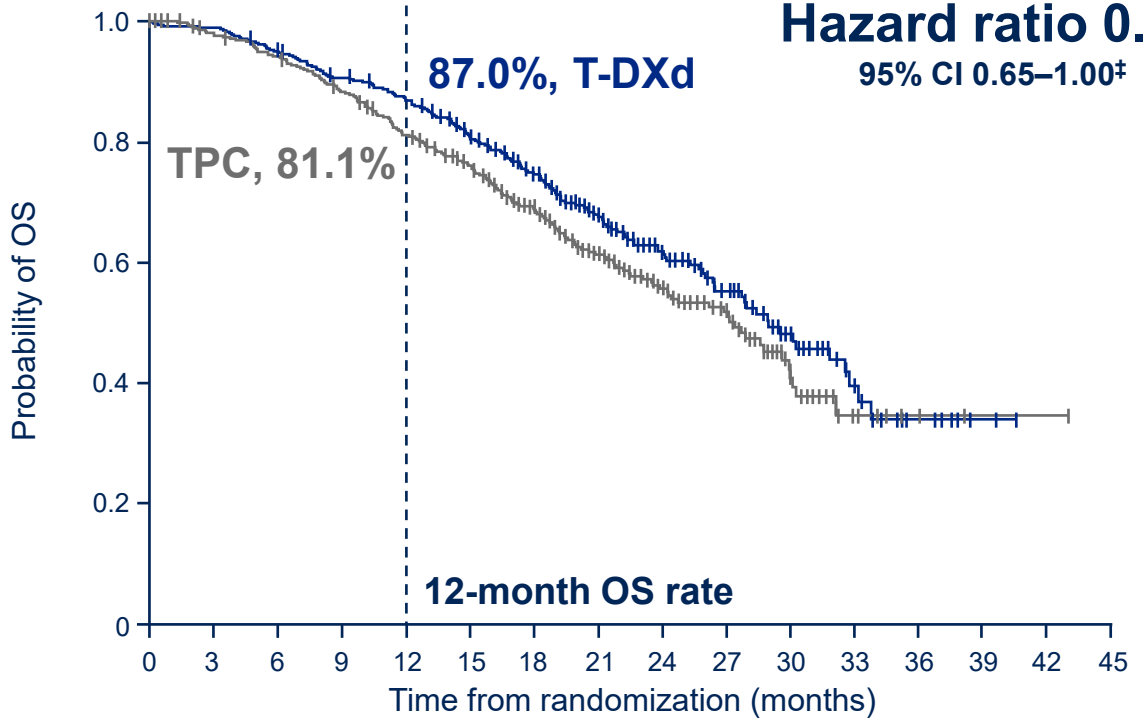
No. at risk

T-DXd	359	354	341	324	309	279	198	140	96	53	32	16	7	2	0	0
TPC	354	333	319	298	273	247	185	126	86	53	23	6	2	1	1	0

20.1% of patients in the TPC group received T-DXd post treatment discontinuation (HER2-low)

ITT (HER2-low + HER2-ultralow)

N=866



T-DXd	436	431	412	391	373	329	235	169	120	69	39	16	7	2	0	0
TPC	430	402	387	360	328	292	210	143	101	62	27	9	3	1	1	0

17.9% of patients in the TPC group received T-DXd post treatment discontinuation (ITT)

*39.6% maturity (of total N for population) at this first interim analysis; median duration of follow up was 18.6 months (HER2-low); †P-value of <0.0046 required for statistical significance; ‡no test of significance was performed in line with the multiple testing procedure; median duration of follow up was 18.2 months (ITT)

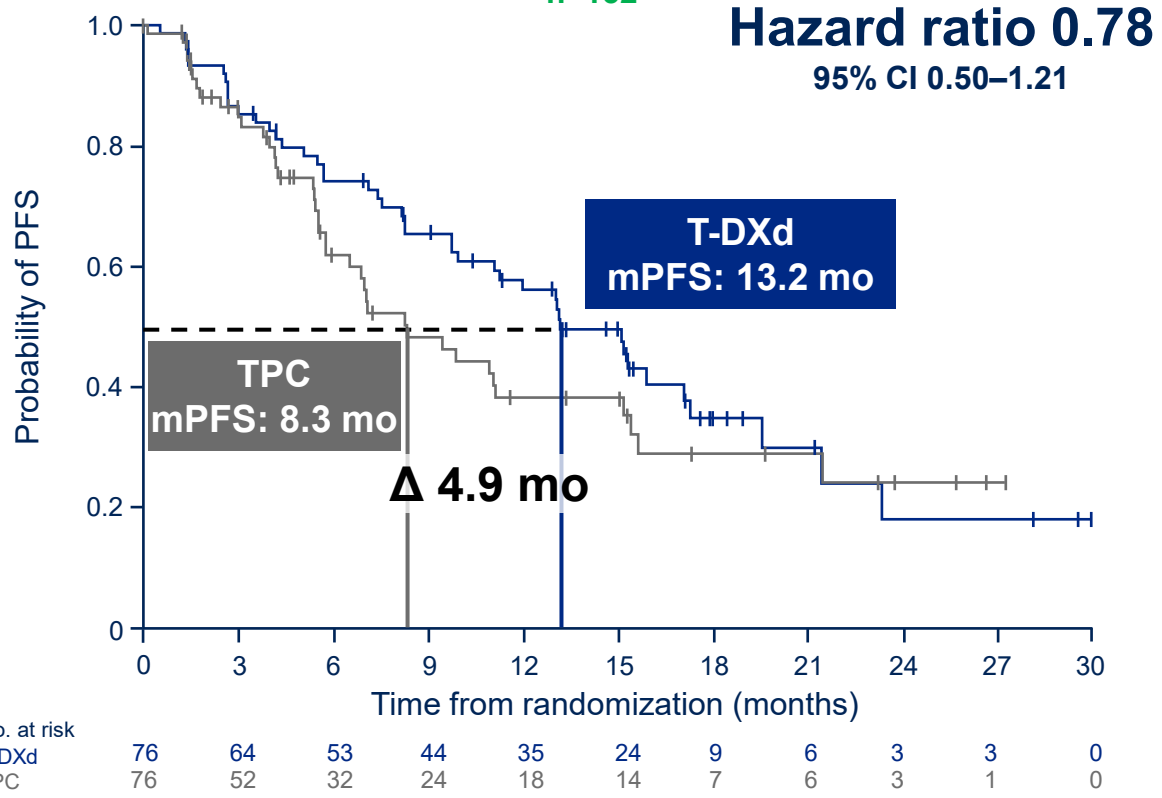
CI, confidence interval; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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PFS and OS in HER2-ultralow: prespecified exploratory analyses

PFS (BICR)

n=152

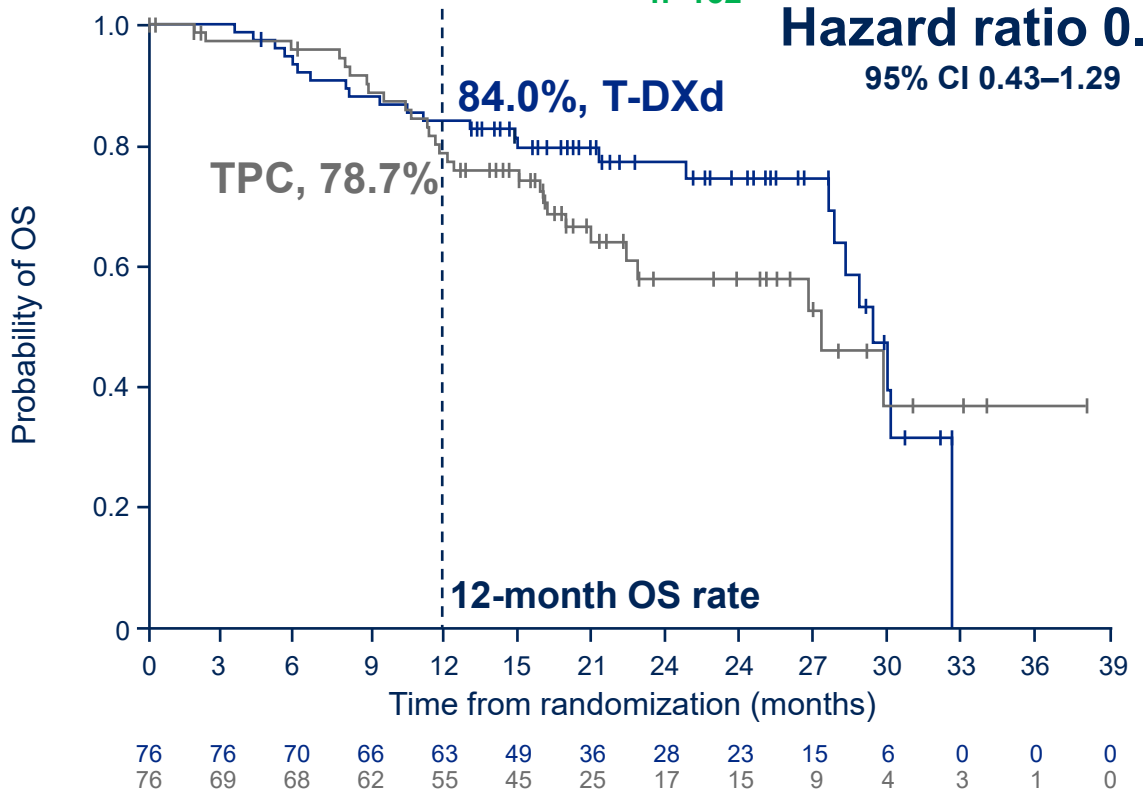


No. at risk

T-DXd	76	64	53	44	35	24	9	6	3	3	0
TPC	76	52	32	24	18	14	7	6	3	1	0

OS*

n=152



76	76	70	66	63	49	36	28	23	15	6	0	0	0
76	69	68	62	55	45	25	17	15	9	4	3	1	0

PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

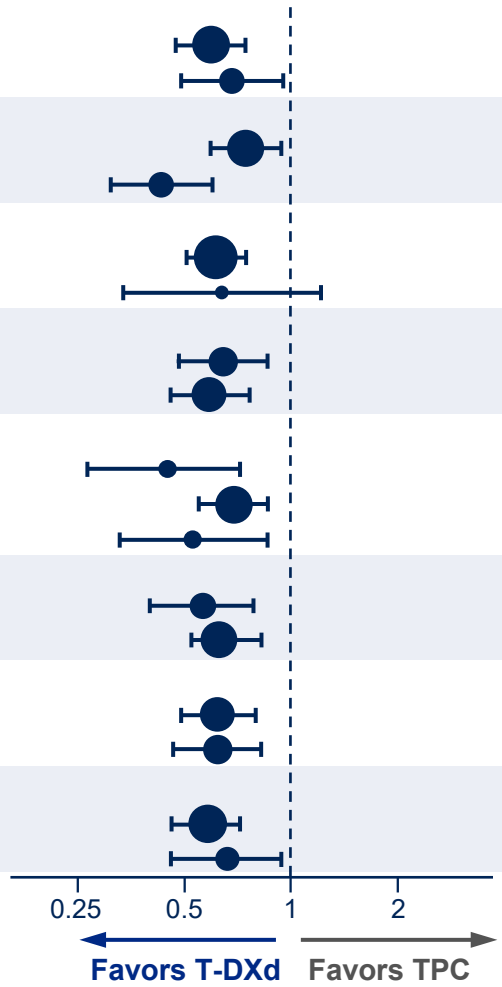
*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months

BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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PFS (BICR) in HER2-low: subgroup analysis

	No. of events / no. of patients		mPFS (95% CI), months		Hazard ratio (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Age					
<65 years	158/252	157/244	13.2 (11.2–15.2)	7.8 (6.9–8.6)	0.59 (0.47–0.74)
≥65 years	67/107	75/110	13.2 (9.7–17.0)	8.5 (6.9–11.5)	0.68 (0.49–0.95)
HER2 status*					
IHC 1+	157/238	150/234	12.9 (11.0–15.2)	8.2 (7.1–9.8)	0.74 (0.59–0.93)
IHC 2+/ISH−	65/117	80/118	15.2 (12.2–21.4)	7.0 (6.2–8.4)	0.43 (0.31–0.60)
Prior CDK4/6i					
Yes	206/324	212/320	13.1 (11.2–15.2)	7.9 (6.9–8.6)	0.61 (0.51–0.74)
No	19/35	20/34	16.1 (9.7–NE)	11.1 (6.9–20.6)	0.64 (0.34–1.21)
Prior taxane use (adjuvant/neoadjuvant setting)					
Yes	94/151	101/151	12.9 (9.7–14.0)	7.4 (6.3–9.3)	0.64 (0.48–0.85)
No	131/208	131/203	15.0 (11.3–16.5)	8.3 (7.0–9.7)	0.59 (0.46–0.76)
Number of prior lines of ET (metastatic setting)					
1	27/54	45/67	15.2 (9.7–19.1)	8.0 (5.7–8.5)	0.45 (0.27–0.72)
2	158/242	153/236	13.1 (11.2–15.2)	8.3 (6.9–10.0)	0.69 (0.55–0.86)
≥3	39/62	33/49	12.3 (8.3–18.5)	8.1 (5.4–9.7)	0.53 (0.33–0.86)
Endocrine resistance					
Primary	66/105	83/116	13.1 (10.0–15.2)	6.8 (5.3–8.1)	0.56 (0.40–0.78)
Secondary	159/254	148/236	13.2 (11.3–15.5)	9.0 (7.5–11.1)	0.65 (0.52–0.82)
Choice of chemotherapy†					
Capecitabine	131/220	134/208	13.5 (11.4–15.4)	8.5 (7.0–11.4)	0.62 (0.49–0.79)
Taxanes (Nab-paclitaxel + paclitaxel)	94/139	98/146	12.9 (9.6–15.4)	7.3 (6.4–8.3)	0.62 (0.46–0.82)
Liver metastases					
Yes	163/243	166/232	11.4 (9.8–13.2)	7.0 (6.4–8.1)	0.58 (0.46–0.72)
No	62/116	66/122	17.0 (15.0–19.4)	11.3 (8.2–14.8)	0.66 (0.46–0.93)



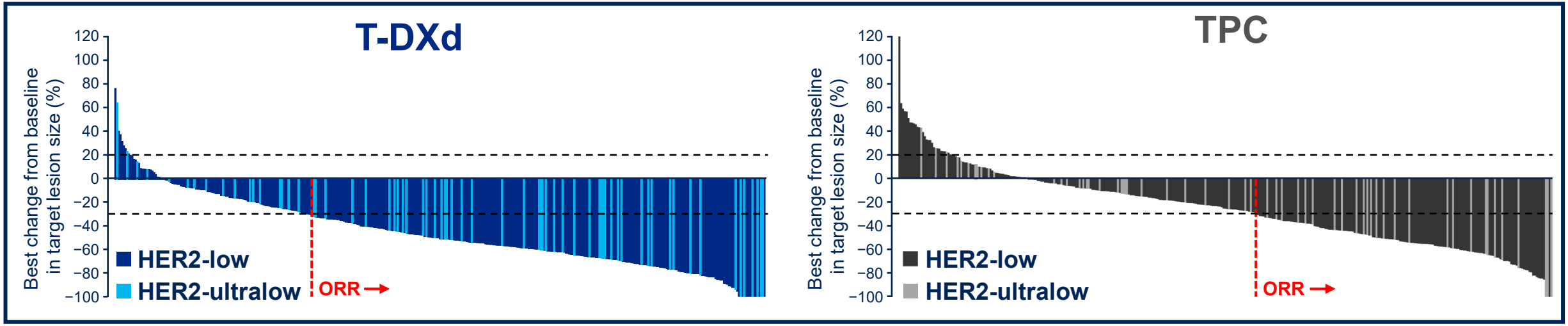
Size of circle is proportional to the number of events

*Based on central laboratory data (ie the HER2 result from the most recent evaluable sample prior to randomization); †specified by the investigator prior to randomization

BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; (m)PFS, (median) progression-free survival; NE, not evaluable; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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Antitumor activity



	HER2-low*		ITT		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
Confirmed ORR, n (%)	**203 (56.5)**	**114 (32.2)**	**250 (57.3)**	**134 (31.2)**	**47 (61.8)**	**20 (26.3)**
Best overall response, n (%)						
Complete response	9 (2.5)	0	13 (3.0)	0	4 (5.3)	0
Partial response	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
Stable disease	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
Clinical benefit rate, n (%)†	275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Median duration of response, mo	14.1	8.6	14.3	8.6	14.3	14.1

ORR based on RECIST v1.1; response required confirmation after 4 weeks
*HER2-low status defined at randomization per IRT data, and HER2-ultralow status defined by central laboratory testing data; †defined as complete response + partial response + stable disease at Week 24, by blinded independent central review
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRT, interactive response technology; ITT, intent-to-treat; mo, months; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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Overall safety summary

	Safety analysis set*	
	T-DXd (n=434)	TPC (n=417)
Total exposure, patient-years	438.5	263.5
Any TEAE, n (%)	429 (98.8)	397 (95.2)
Treatment-related TEAEs, n (%)	417 (96.1)	373 (89.4)
Grade ≥3	176 (40.6)	131 (31.4)
Serious TEAEs, n (%)	88 (20.3)	67 (16.1)
TEAEs associated with treatment discontinuation, n (%)	62 (14.3)	39 (9.4)
TEAEs associated with dose interruptions, n (%)	210 (48.4)	160 (38.4)
TEAEs associated with dose reductions, n (%)	107 (24.7)	161 (38.6)
TEAEs leading to death, n (%)	11 (2.5)	6 (1.4)
Treatment related (investigator assessed)‡	5 (1.2)	0

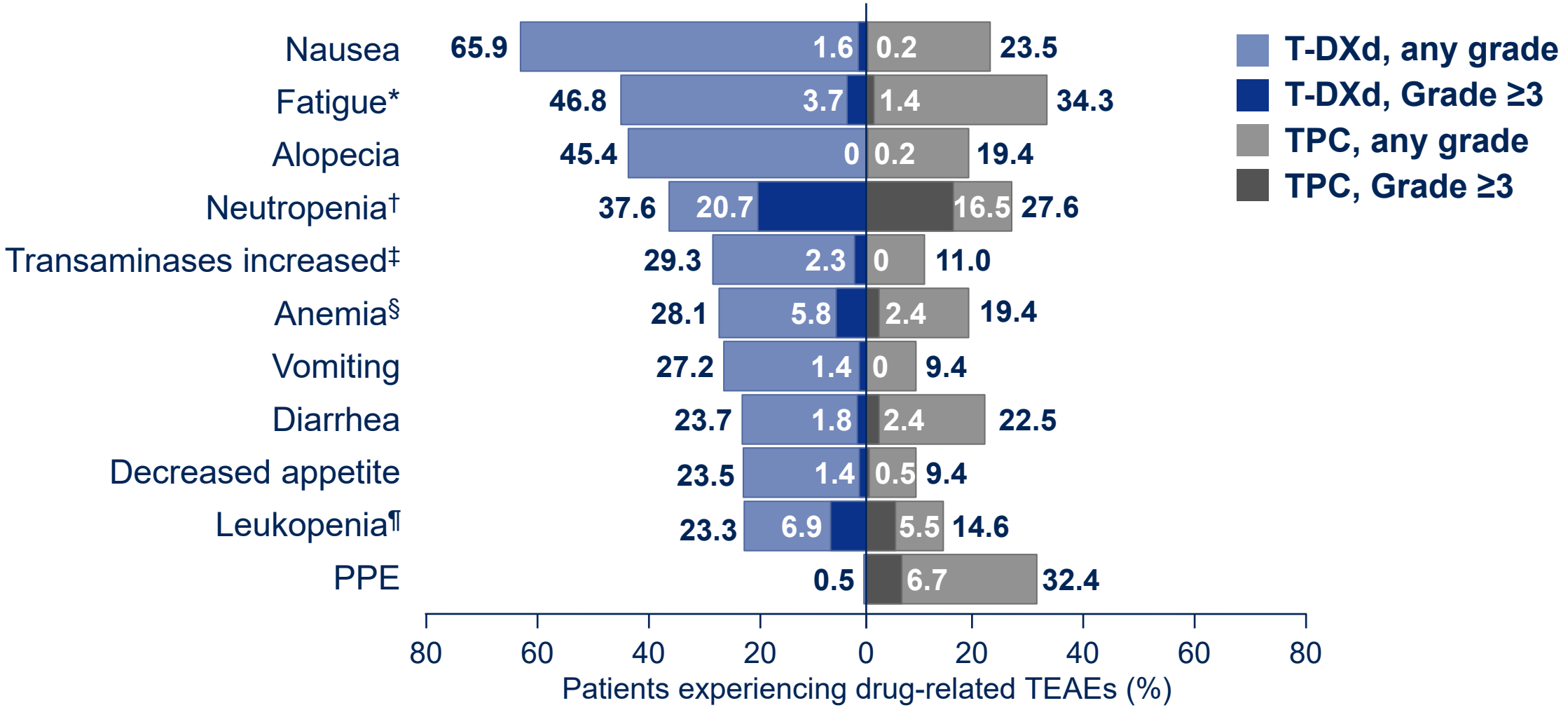
- **Median treatment duration:**
  - **T-DXd: 11.0 mo (range 0.4–39.6)**
  - **TPC: 5.6 mo (range 0.1–35.9)**
- Most common TEAE associated with treatment discontinuation:
  - T-DXd: 5.3%, pneumonitis†
  - TPC: 1.4%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction:
  - T-DXd: 4.4%, nausea
  - TPC: 16.5%, PPE

*Safety analyses included all patients who received at least one dose of study treatment; †in the T-DXd group, 3.5% of patients discontinued due to interstitial lung disease; ‡reasons were interstitial lung disease (n=2), sepsis (n=1), neutropenic sepsis (n=1) and general physical health deterioration (n=1)
mo, months; PPE, palmar-plantar erythrodysesthesia; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, chemotherapy treatment of physician's choice

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Drug-related TEAEs in ≥20% of patients (either treatment group)



*Includes the preferred terms fatigue, asthenia, malaise, and lethargy; †includes the preferred terms neutrophil count decreased and neutropenia; ‡includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increased; §includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased; ¶includes the preferred terms white blood cell count decreased and leukopenia

PPE, palmar-plantar erythrodysesthesia; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, chemotherapy treatment of physician's choice

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Adverse events of special interest

Adjudicated as drug-related interstitial lung disease / pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n=434)	7 (1.6)	36 (8.3)	3 (0.7)	0	3 (0.7)	49 (11.3)
TPC (n=417)	0	1 (0.2)	0	0	0	1 (0.2)

Left ventricular dysfunction†

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Ejection fraction decreased						
T-DXd (n=434)	1 (0.2)	31 (7.1)	3 (0.7)	0	0	35 (8.1)
TPC (n=417)	0	11 (2.6)	1 (0.2)	0	0	12 (2.9)
Cardiac failure						
T-DXd (n=434)	0	0	0	0	0	0
TPC (n=417)	0	1 (0.2)	1 (0.2)	1 (0.2)	0	3 (0.7)

*Grouped term. Median time to first onset of interstitial lung disease / pneumonitis for patients with T-DXd was 141 days (range 37–835). No pending cases of drug-related interstitial lung disease / pneumonitis to be adjudicated. One interstitial lung disease–related death per investigator assessment was upheld by the adjudication committee. An additional two deaths were adjudicated as interstitial lung disease–related by the adjudication committee; †data for the most common preferred terms are shown on the slide; additionally, one patient in each treatment group had the preferred term left ventricular dysfunction (Grade 3 with T-DXd, Grade 2 with TPC)
T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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Future analyses and research questions

- Clinical validation of diagnostics and HER2-ultralow cutoffs
- Additional subgroup analyses
- Biomarkers and translational analyses
- Patient-reported outcomes
- Identification of the lower HER2 expression threshold in mBC tumors where clinically meaningful T-DXd efficacy is observed (DESTINY-Breast15)

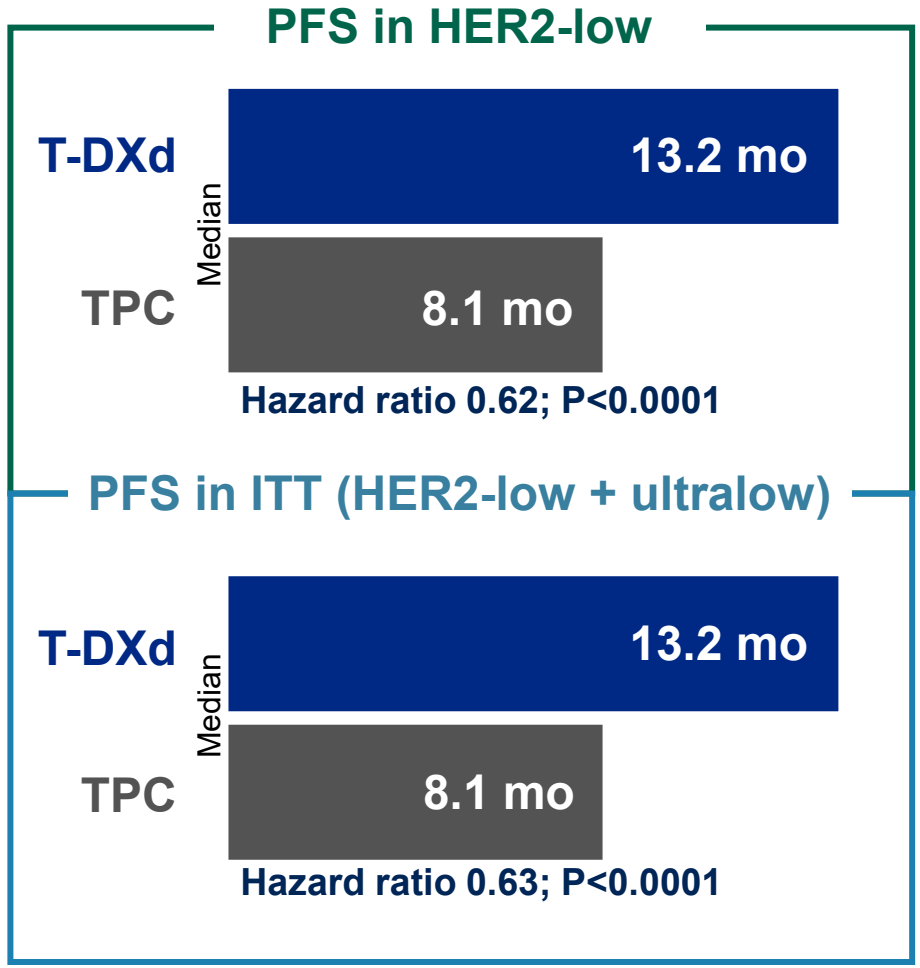
HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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Conclusions

- T-DXd demonstrated a statistically significant and clinically meaningful PFS benefit vs TPC (chemotherapy) in HR+, HER2-low mBC in an earlier line of treatment than DESTINY-Breast04
- Results in HER2-ultralow were consistent with HER2-low
- Confirmed ORR was 57.3% (T-DXd) vs 31.2% (TPC) in ITT
- No new safety signals were identified; interstitial lung disease remains an important safety risk of T-DXd

DESTINY-Breast06 establishes T-DXd as an effective new treatment option for patients with HR+, HER2-low and HER2-ultralow mBC following ≥1 endocrine-based therapy



HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; ITT, intent-to-treat; mBC, metastatic breast cancer; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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Supplementary content is available:
- Plain language summary infographic
- ASCO patient summary

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