ASCO 2024 Presentation Materials

- **DESTINY-Breast06**
  - Curigliano, G. et al., ASCO 2024 #LBA1000 Oral
- **DESTINY-Breast03**
  - Hamilton, E. et al., ASCO 2024 #1025 Poster
- **DESTINY-Breast07**
  - André, F. et al., ASCO 2024, #1009 Oral
- **DESTINY-Lung02**
  - Jänne, P. A. et al., ASCO 2024, #8543 Poster
- **TROPION-Lung02**
  - Levy, B. et al., ASCO 2024, #8617 Poster

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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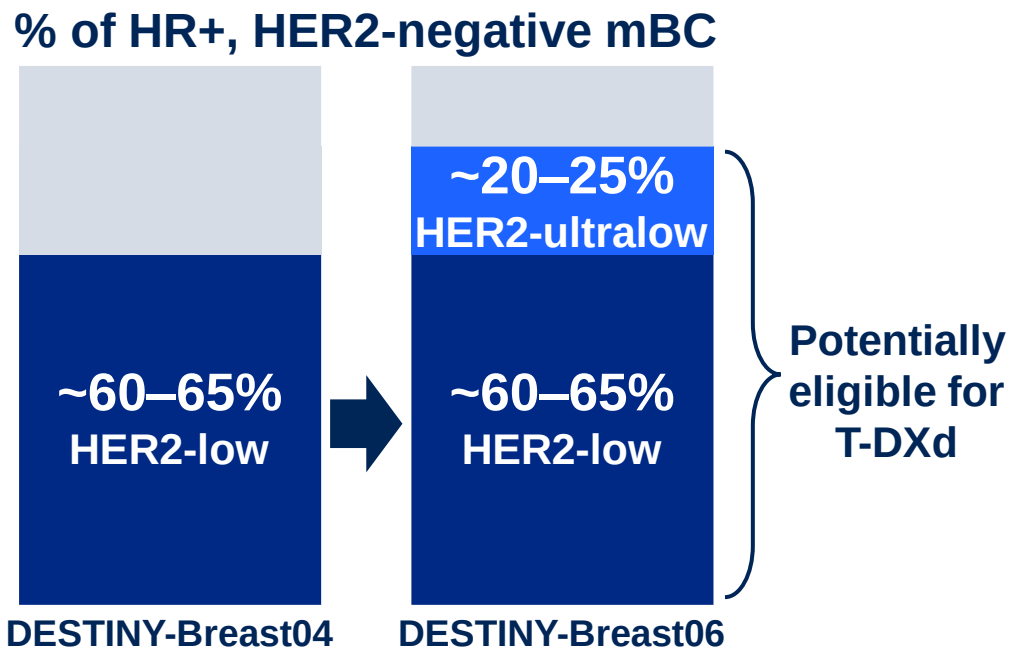
On behalf of the DESTINY-Breast06 investigators

DESTINY-Breast06: key takeaways



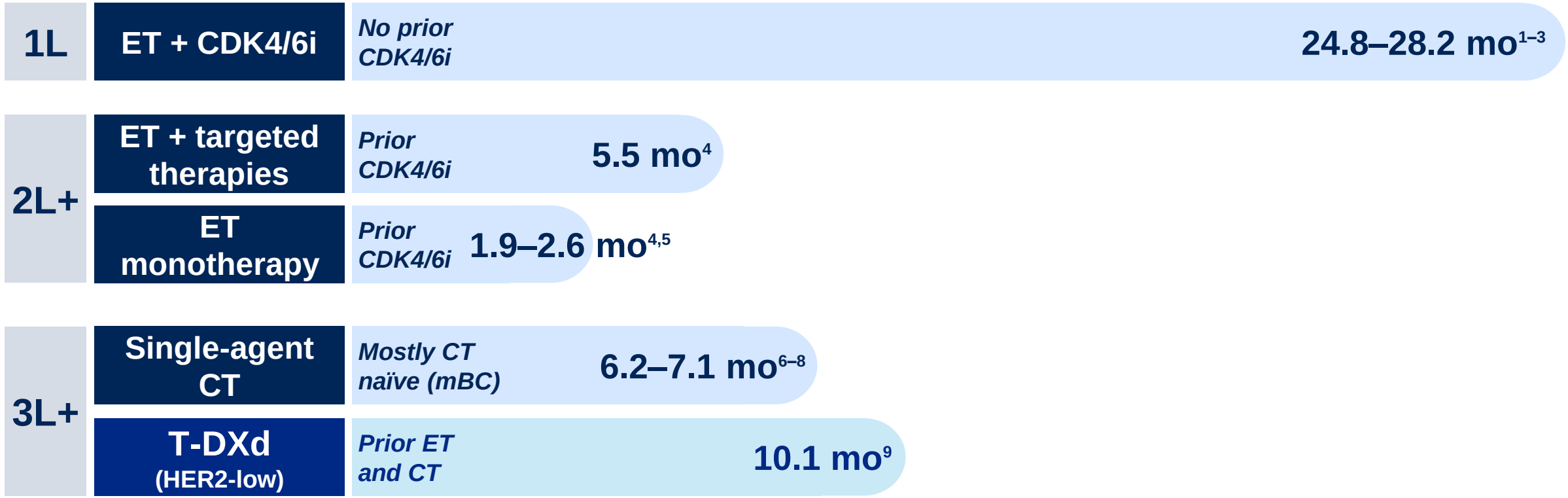
- T-DXd demonstrated efficacy in **HER2-low mBC** in an **earlier line of treatment** to DESTINY-Breast04
- Including HER2-ultralow, the proportion of patients who could benefit from T-DXd is **~85% of HR+, HER2-negative mBC** after DESTINY-Breast06

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

Unmet treatment need in HR+, HER2-negative mBC

Current treatment landscape and outcomes: mPFS*



*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

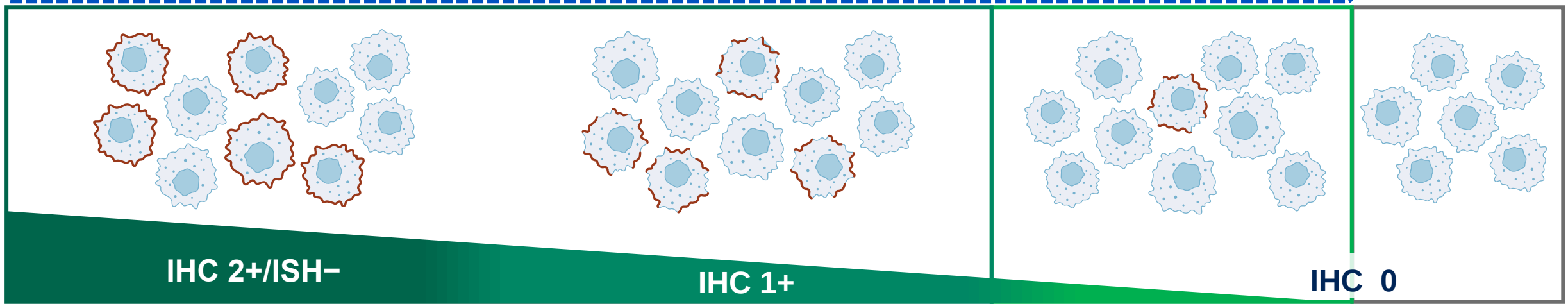
Targeting ‘low’ and ‘ultralow’ HER2-expressing tumors in mBC

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

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

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)

R 1:1

T-DXd
5.4 mg/kg Q3W
(n=436)

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

Options: capecitabine, nab-paclitaxel, paclitaxel

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)

Statistical analysis

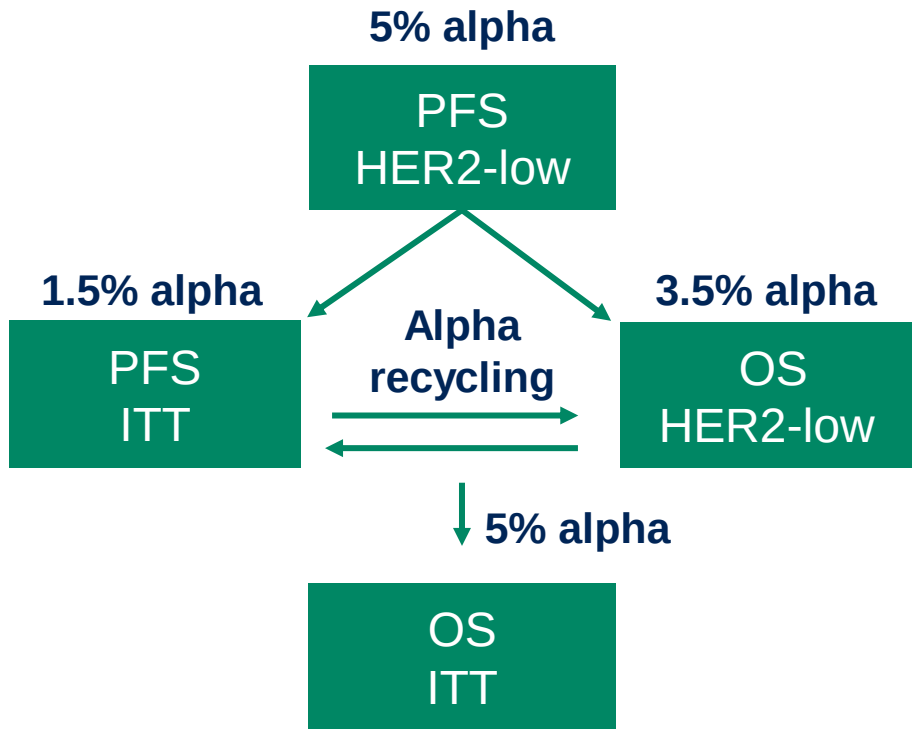
PFS primary analysis by BICR (HER2-low)
(planned after approximately 456 events)

- 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)

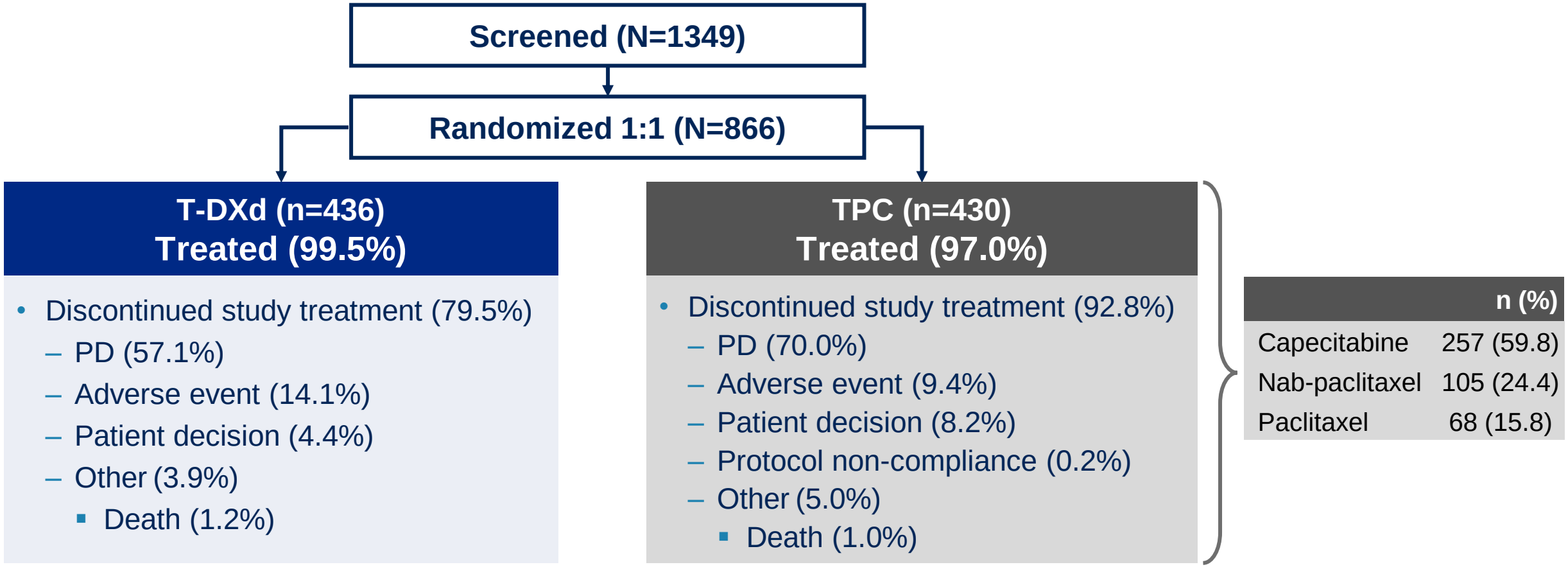
- At DCO, there were 282 events in the HER2-low and 335 events in the ITT (HER2-low + -ultralow) **(maturity: ~40% of total N)**
- Second interim and final OS analyses will be performed in HER2-low at ~56% and ~74% maturity, respectively

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

Patient disposition



	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

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

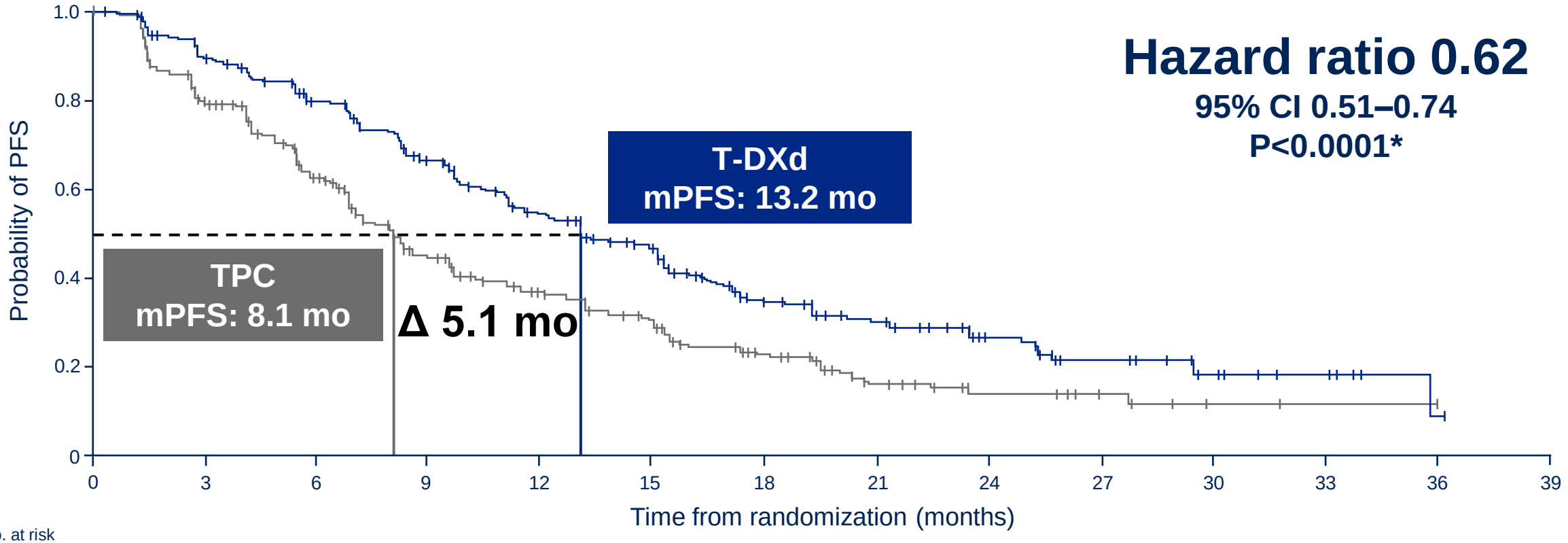
Prior therapies

	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

PFS (BICR) in HER2-low: primary endpoint



Hazard ratio 0.62
95% CI 0.51–0.74
P<0.0001*

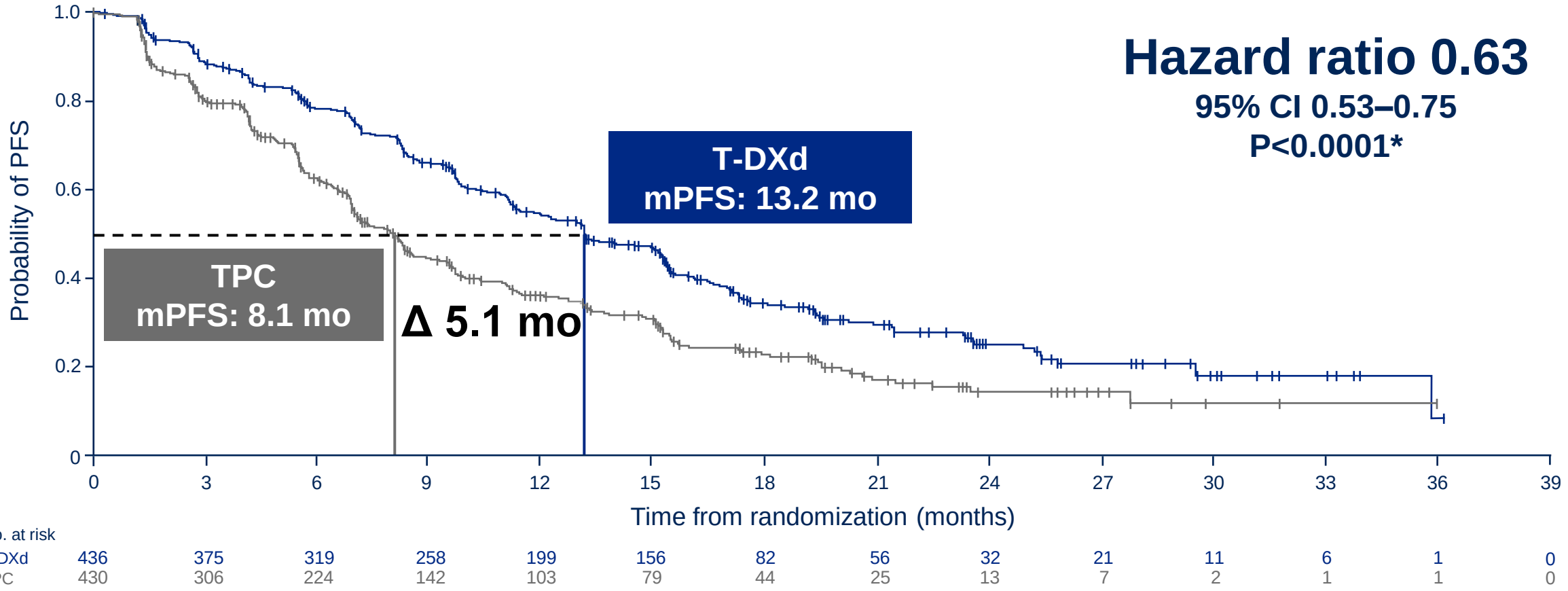
No. at risk

T-DXd	359	310	265	213	163	131	72	49	28	17	10	6	1	0
TPC	354	254	192	118	85	65	37	19	10	6	2	1	1	0

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

PFS (BICR) in ITT: key secondary endpoint



Hazard ratio 0.63
95% CI 0.53–0.75
P<0.0001*

No. at risk

T-DXd	436	375	319	258	199	156	82	56	32	21	11	6	1	0
TPC	430	306	224	142	103	79	44	25	13	7	2	1	1	0

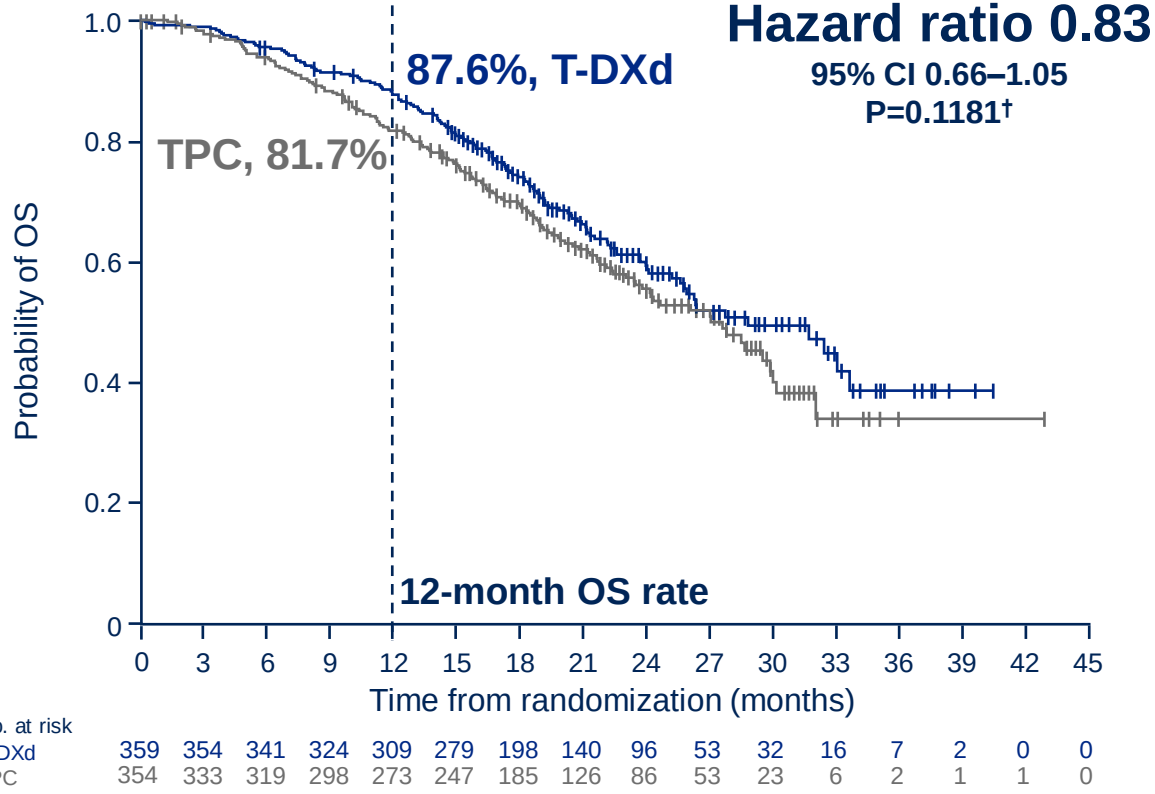
T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in ITT

*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

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

HER2-low*

n=713



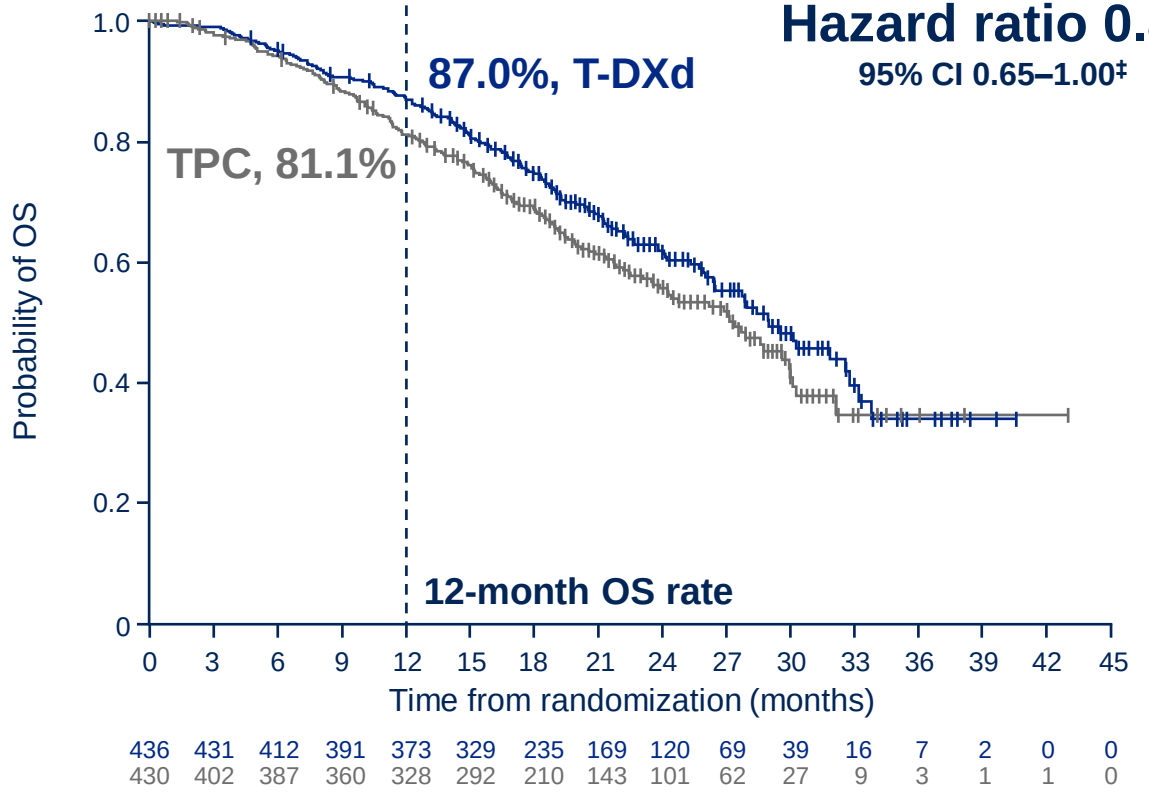
No. at risk

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)

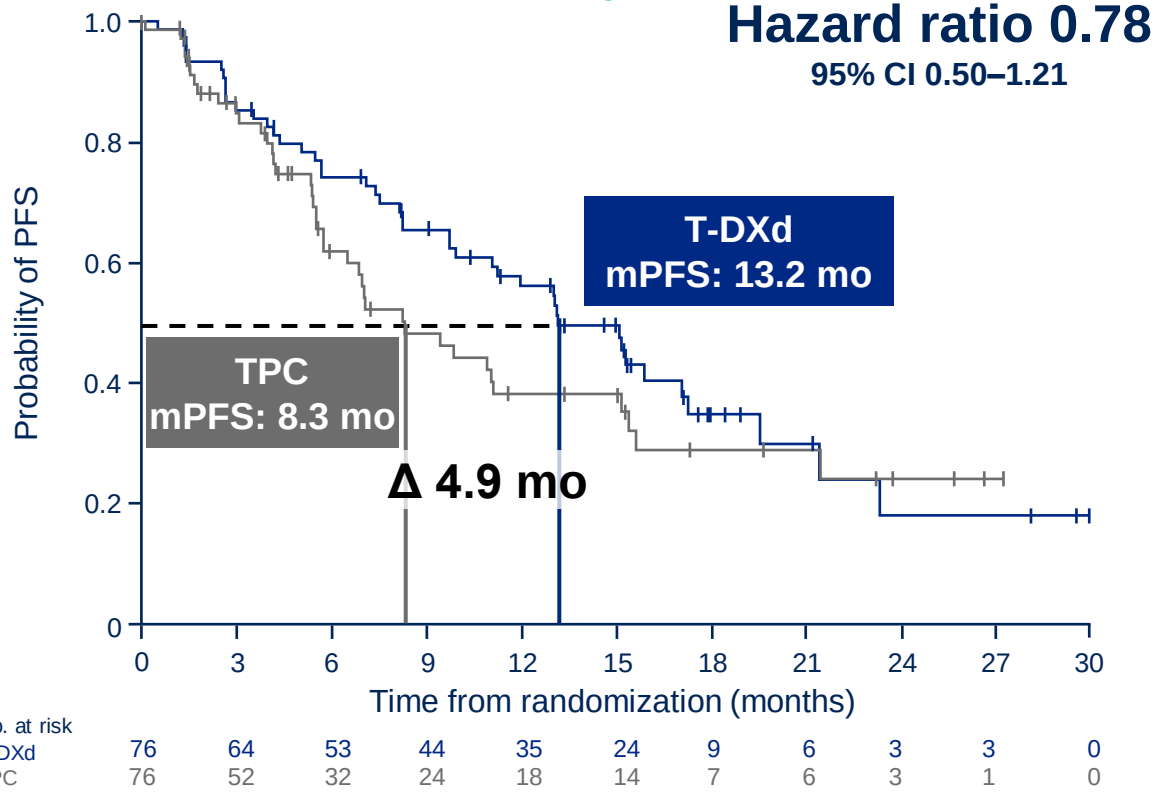
*39.6% maturity (of total N for population) at this first interim analysis; median duration of follow up was 18.6 months (HER2-low); †P-value of <0.0046 required for statistical significance; ‡no test of significance was performed in line with the multiple testing procedure; median duration of follow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

PFS and OS in HER2-ultralow: prespecified exploratory analyses

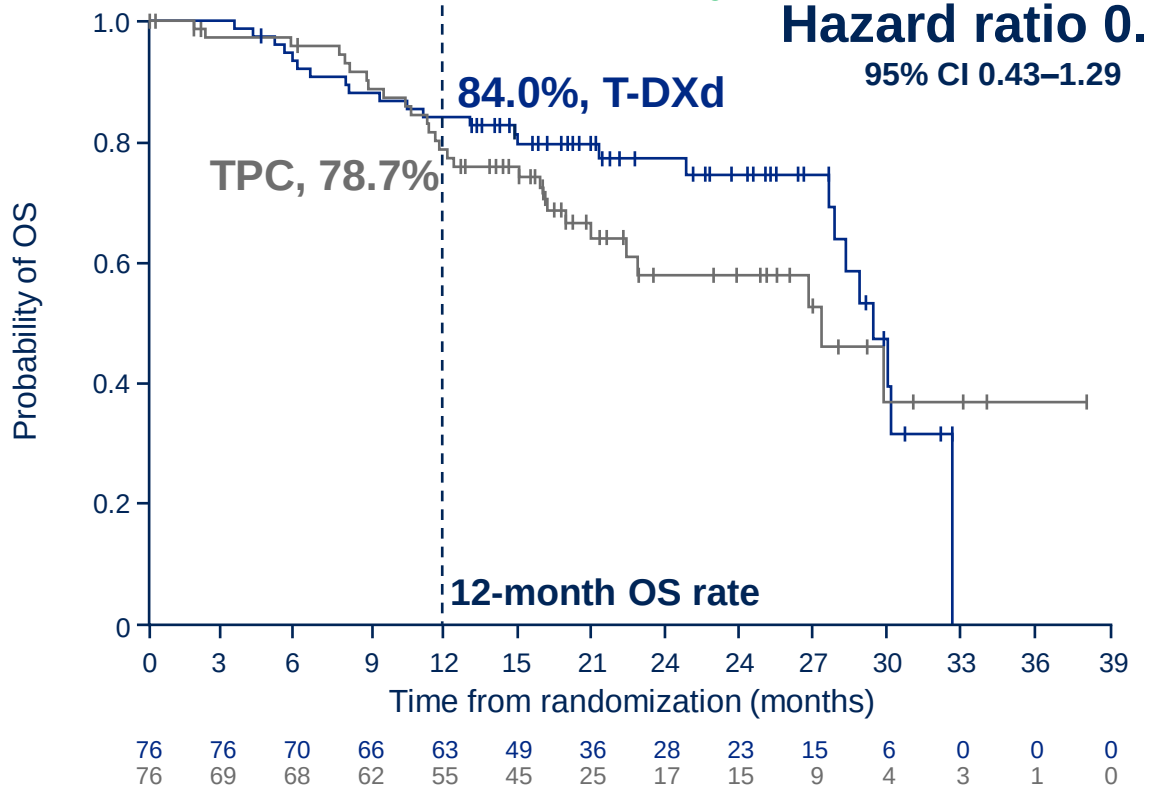
PFS (BICR)

n=152



OS*

n=152



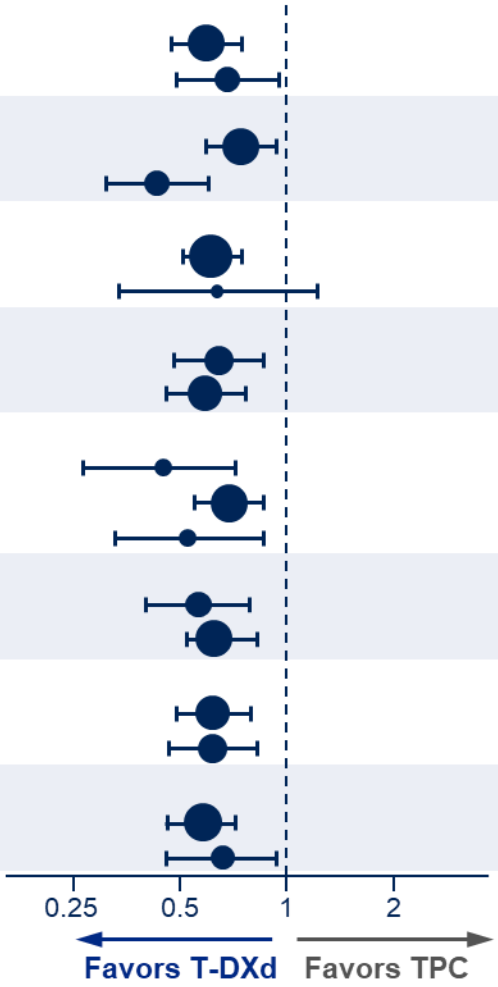
PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*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

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)

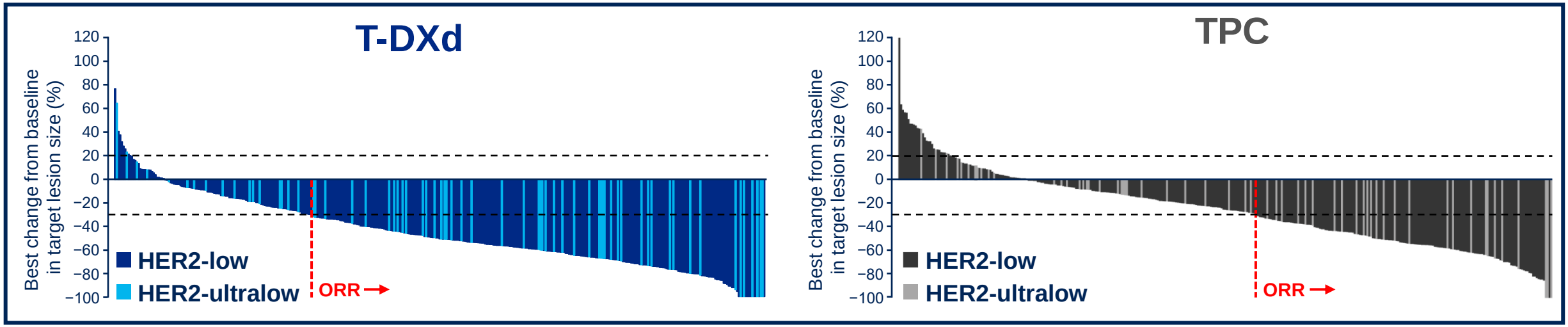


Size of circle is proportional to the number of events

*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

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

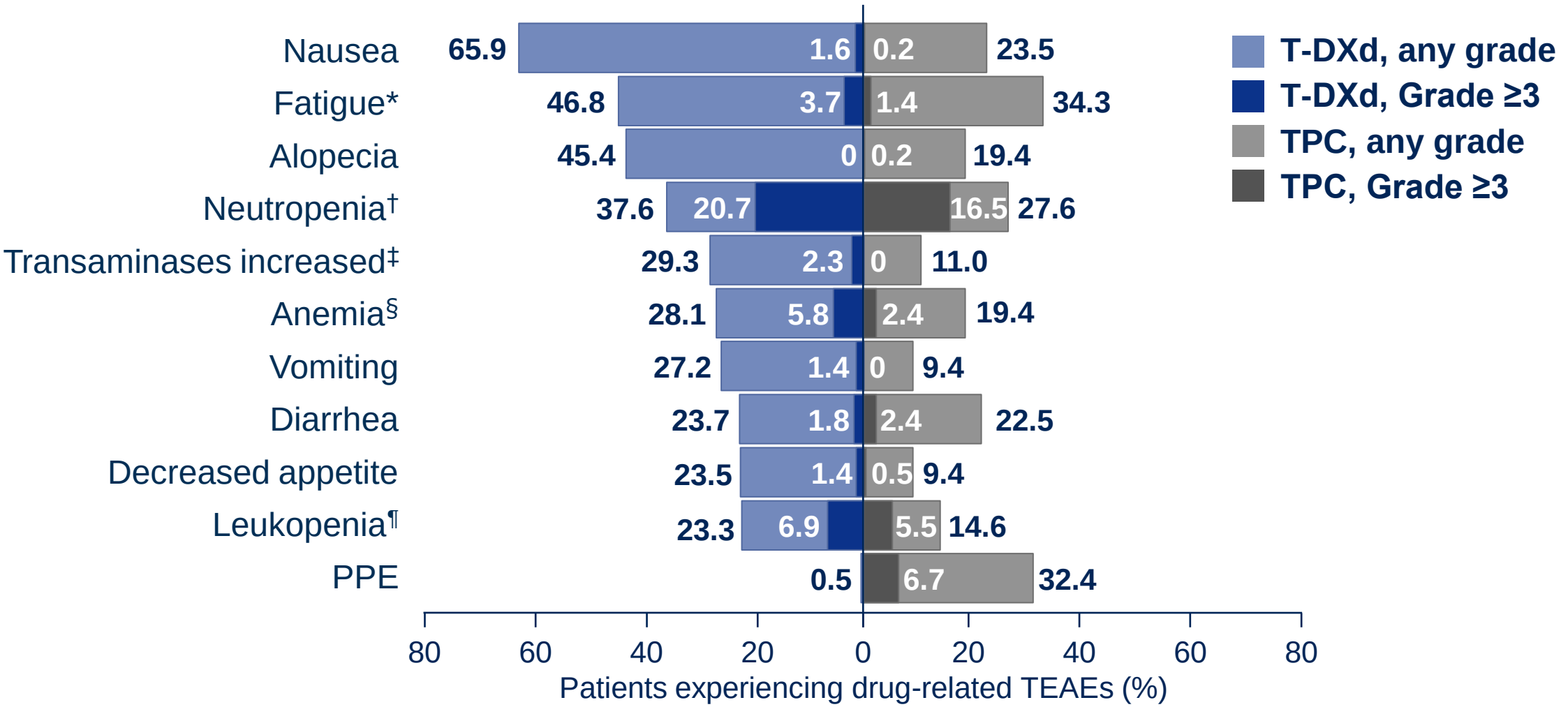
Overall safety summary

	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

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

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

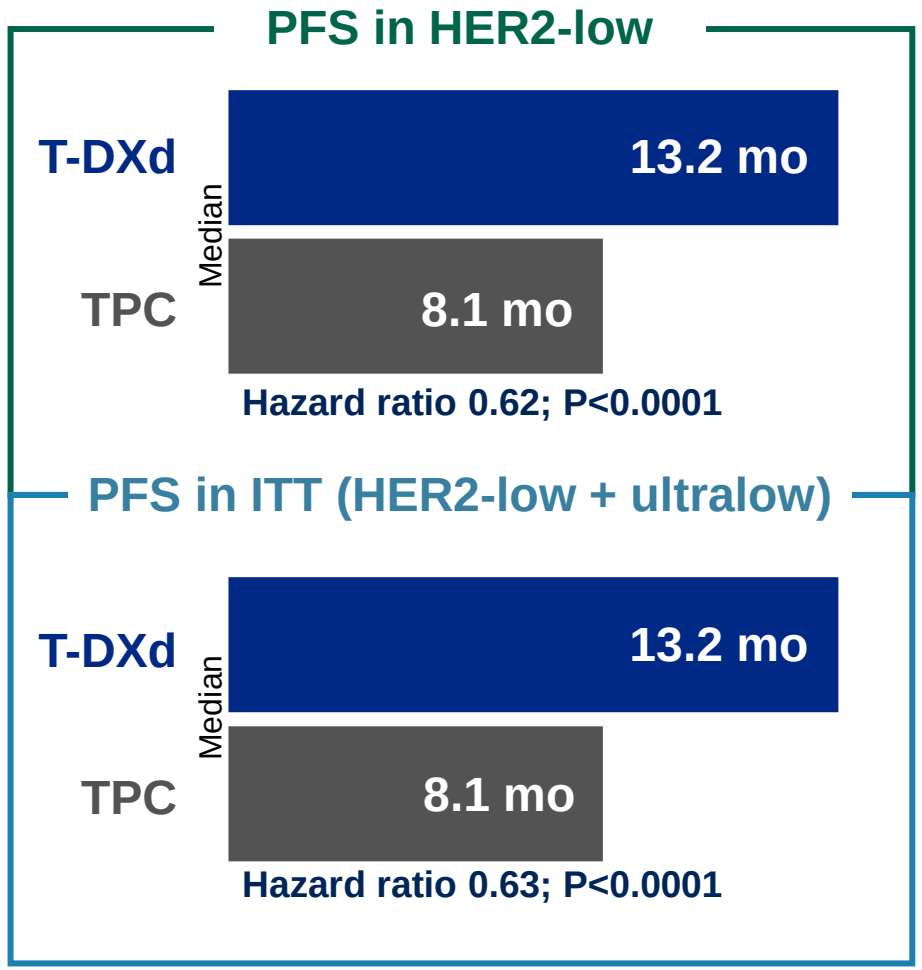
Future analyses and research questions

- 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)

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

Trastuzumab Deruxtecan Versus Trastuzumab Emtansine in Patients With HER2-Positive Metastatic Breast Cancer: Updated Survival Results of DESTINY-Breast03

Accompanying article in press in *Nature Medicine*: Cortés J et al. https://bit.ly/CortesNatMed

Erika Hamilton,[1] Sara A. Hurvitz,[2] Seock-Ah Im,[3] Hiroji Iwata,[4] Giuseppe Curigliano,[5,6] Sung-Bae Kim,[7] Joanne W. Y. Chiu,[8] Jose L. Pedrini,[9] Wei Li,[10] Kan Yonemori,[11] Giampaolo Bianchini,[12] Sherene Loi,[13] Giuliano S. Borges,[14] Xian Wang,[15] Thomas Bachelot,[16] Shunsuke Nakatani,[17] Shahid Ashfaque,[18] Zhengkang Liang,[18] Anton Egorov,[19] Javier Cortés[20]

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Objective

- To report updated efficacy and safety results from DESTINY-Breast03, a phase 3 trial of trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC) previously treated with trastuzumab and a taxane

Conclusions

- Results of this long-term follow-up further support previously demonstrated superiority of T-DXd over T-DM1 for the treatment of patients with HER2-positive mBC whose disease progressed after trastuzumab and taxane
  - Confirmed objective response rate (cORR) by investigator was 78.9% for T-DXd and 36.9% for T-DM1
  - Median progression-free survival (PFS) by investigator was ~4 times longer for T-DXd (29.0 months) versus T-DM1 (7.2 months)
  - Median overall survival (OS) was reached in this updated analysis with an approximate 10 month improvement over T-DM1 with T-DXd; the risk of death was reduced by 27% (hazard ratio [HR], 0.73)
- Despite longer treatment duration, the safety profile of T-DXd remained manageable, with no cumulative toxicities observed with longer follow-up, and was consistent with the previous analyses[1,2]
  - Adjudicated drug-related interstitial lung disease (ILD)/pneumonitis occurred in 16.7% of patients in the T-DXd group and 3.4% of patients in the T-DM1 group; there were no grade 4 or 5 events in either group
- These data continue to support the use of T-DXd as standard of care in patients with HER2-positive mBC whose disease progressed after trastuzumab and taxane and show the longest OS in this setting

Plain Language Summary

Why did we perform this research?
Approximately 20% of breast cancers express high levels of a protein called human epidermal growth factor receptor 2 (HER2).[1,2] Trastuzumab deruxtecan (T-DXd) is an anticancer therapy that targets HER2.[3,4] DESTINY-Breast03 was performed to compare the treatment benefits and safety of T-DXd with trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer that cannot be removed by surgery (unresectable) and/or has spread to other areas of the body (metastatic).[5,6] Previous results from DESTINY-Breast03 showed T-DXd to be more beneficial in patients than T-DM1.[5,6] The objective of the current analysis was to evaluate the treatment benefits and safety of T-DXd compared with T-DM1 after a longer follow-up in patients participating in DESTINY-Breast03.

How did we perform this research?
In the DESTINY-Breast03 study, 524 patients with unresectable or metastatic breast cancer were randomly given either T-DXd 5.4 mg/kg (n = 261) or T-DM1 3.6 mg/kg (n = 263). Because a significant treatment benefit was shown with T-DXd versus T-DM1 in previous results,[5,6] the current updated analysis is exploratory, and the efficacy results were assessed by the investigators.

What were the findings of this research?
T-DXd had better treatment benefits compared with T-DM1. The length of time (middle in a range) that patients lived with their cancer before the disease got worse or caused death (also known as median progression-free survival) was 4 times longer in patients treated with T-DXd than in those treated with T-DM1 (29 and 7 months, respectively). The length of time (middle in a range) that patients survived after starting study treatment (known as median overall survival) was approximately 10 months longer in the T-DXd group than in the T-DM1 group (about 4.4 and 3.6 years, respectively). In addition, the safety profile of T-DXd remained manageable in this longer follow-up, with no increase in side effects observed over time. Adjudicated drug-related interstitial lung disease/pneumonitis, which is an adverse event of interest for T-DXd, occurred in 17% of patients in the T-DXd group and 3% of patients in the T-DM1 group since the beginning of the study; there were no grade 4 or 5 events in either group.

What were the implications of this research?
Findings from this longer follow-up were mostly similar to previous results;[5,6] and continue to support the use of T-DXd as standard of care in patients with HER2-positive metastatic breast cancer whose disease progressed after trastuzumab and taxane.

Where can I access more information?
To learn more about the DESTINY-Breast03 study, you can visit https://clinicaltrials.gov/ct2/show/NCT03529110

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5. Cortés J et al. *N Engl J Med.* 2022;386(12):1143-1154.
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Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2024; Chicago, Illinois

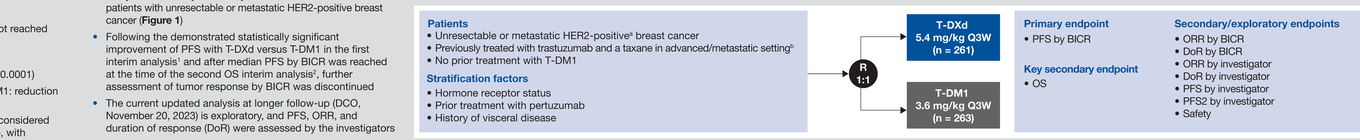
Introduction

- DESTINY-Breast03 (NCT03529110) was conducted to investigate the efficacy and safety of T-DXd versus T-DM1 in patients with HER2-positive mBC previously treated with trastuzumab and taxane[1,2]
  - **First interim analysis (data cutoff [DCO], May 21, 2021)[1]**
    - Primary endpoint (PFS by blinded independent central review [BICR]) was met: median PFS was not reached for T-DXd versus 6.8 months for T-DM1 (HR, 0.28; $P < 0.001$)
  - **Second OS interim analysis (DCO, July 25, 2022)[2]**
    - Median PFS by BICR: 28.8 months for T-DXd versus 6.8 months for T-DM1 (HR, 0.33; nominal $P < 0.0001$)
    - T-DXd demonstrated statistically significant and clinically meaningful OS improvement versus T-DM1: reduction in the risk of death was approximately 36% (HR, 0.64; $P = 0.0037$)
- Based on the strength of DESTINY-Breast03 efficacy and safety data, T-DXd was approved[3] and is now considered the preferred standard (guideline-recommended) treatment after progression on taxane and trastuzumab, with T-DM1 as an alternative option[4]
- Because median OS was not reached in either treatment group at the first or second OS interim analyses, we report this updated analysis after a median follow-up of 41 months[1,2]

Methods

- DESTINY-Breast03 was an open-label, multicenter, phase 3 study of the efficacy and safety of T-DXd versus T-DM1 in patients with unresectable or metastatic HER2-positive breast cancer (**Figure 1**)
- Following the demonstrated statistically significant improvement of PFS with T-DXd versus T-DM1 in the first interim analysis[1] and after median PFS by BICR was reached at the time of the second OS interim analysis[2], further assessment of tumor response by BICR was discontinued
- The current updated analysis at longer follow-up (DCO, November 20, 2023) is exploratory, and PFS, ORR, and duration of response (DoR) were assessed by the investigators

Figure 1. DESTINY-Breast03: Study Design[1,2]



[a]HER2 IHC 3+ or IHC 2+/ISH+ based on central confirmation.
[b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane.

Abbreviations
ADC, antibody-drug conjugate; AE, adverse event; BICR, blinded independent central review; cORR, confirmed objective response rate; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cutoff; DoR, duration of response; EAIRs, exposure-adjusted incidence rates; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; mBC, metastatic breast cancer; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival from time of randomization to progression on the next line of therapy or death; PR, partial response; OS, overall survival; RPSFTM, rank-preserving structure failure time model; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

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1. Cortés J et al. *N Engl J Med.* 2022;386(12):1143-1154.
2. Hurvitz SA et al. *Lancet.* 2023;401(10371):105-117.
3. FDA Press Release. May 4, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-fam-trastuzumab-deruxtecan-nxki-breast-cancer.
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Acknowledgments
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Disclosures
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Results

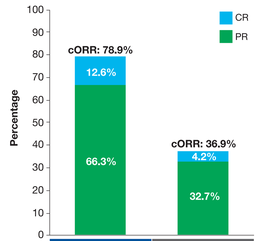
Patients

- As of November 20, 2023, 50 patients (19.5%) in the T-DXd group and 10 patients (3.8%) in the T-DM1 group remained on treatment
  - The most common reasons patients discontinued study treatment were progressive disease (41.6% [T-DXd] and 70.1% [T-DM1]) and adverse events (23.7% [T-DXd] and 9.2% [T-DM1])
- Median duration of follow-up was 43.0 months (range, 0.0-62.9 months) in the T-DXd group and 35.4 months (range, 0.0-60.9 months) in the T-DM1 group
- Patient baseline demographics and characteristics were similar in both treatment groups[1,2]
  - The median age was 54.3 years (range, 27.9-83.1 years) in the T-DXd group and 54.2 years (range, 20.2-83.0 years) in the T-DM1 group
  - The majority of patients in both groups had a HER2 IHC score of 3+ (T-DXd, 89.7% and T-DM1, 88.2%)
  - Patients had received a median of two prior lines of therapy in the metastatic setting in both treatment groups

Efficacy by Investigator Assessment

- cORR (**Figure 2**) and median PFS by investigator assessment (**Figure 3**) were consistent with the previous analyses[1,2]
  - The PFS rate at 36 months was 45.7% with T-DXd and 12.4% with T-DM1

Figure 2. cORR and DoR by Investigator Assessment

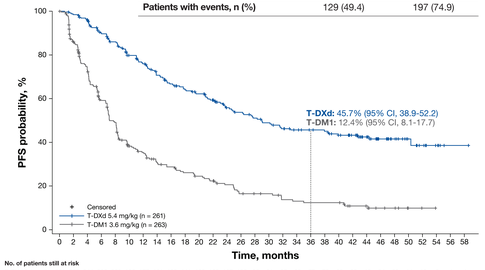


	T-DXd n = 261	T-DM1 n = 263
cORR,[a] n (%) (95% CI)[b]	206 (78.9) (73.5-83.7)	97 (36.9) (31.0-43.0)
CR, n (%)	33 (12.6)	11 (4.2)
PR, n (%)	173 (66.3)	86 (32.7)
SD, n (%)	48 (18.4)	119 (45.2)
PD, n (%)	2 (0.8)	34 (12.9)
NE, n (%)	5 (1.9)	13 (4.9)
Median DoR,[a,c] months (95% CI)	30.5 (23.0-NE)	17.0 (14.1-23.7)
DoR rate at 36 months, % (95% CI)	48.9 (41.3-56.1)	28.7 (18.9-39.2)

[a]By investigator assessment.
[b]Based on Clopper-Pearson method for single proportion and for the difference of 2 proportions with continuity correction.
[c]Median is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method.

Figure 3. PFS by Investigator Assessment

	T-DXd n = 261	T-DM1 n = 263
Median (95% CI), months	29.0 (23.7-40.0)	7.2 (6.8-8.3)
HR (95% CI)	0.30 (0.24-0.38)	
Patients with events, n (%)	129 (49.4)	197 (74.9)



No. of patients still at risk
T-DXd 5.4 mg/kg (n = 261): 261 252 244 222 209 188 177 161 150 141 135 123 107 102 96 91 85 80 77 75 68 62 48 34 23 14 10 5 1 1 1
T-DM1 3.6 mg/kg (n = 263): 263 216 175 136 111 80 72 60 55 49 45 41 35 28 26 25 20 19 18 18 18 12 11 7 6 2 1 0

Post-Trial Anticancer Systemic Treatment

- Of the patients who discontinued treatment in the T-DXd and T-DM1 groups, 144 and 198 patients, respectively, received post-trial anticancer systemic therapy (**Table 1**)
- Median PFS from time of randomization to progression on the next line of therapy or death (PFS2) per investigator assessment was 45.2 months (95% CI, 39.3 months-NE) for T-DXd and 23.1 months (95% CI, 17.8-29.7 months) for T-DM1 (HR, 0.53; 95% CI, 0.41-0.68)

Table 1. Post-Trial Anticancer Systemic Treatment

	T-DXd n = 261	T-DM1 n = 263
Patients who discontinued study treatment,[a] n (%)	207 (80.5)	251 (96.2)
Patients assigned to undergo surgery[b]	6 (2.9)	15 (6.0)
Patients assigned to receive radiation treatment[b]	26 (12.6)	43 (17.1)
Patients assigned to receive post-trial anticancer systemic treatment[b]	144 (69.6)	198 (78.9)
Type of post-trial anticancer systemic treatment,[c] n (%)		
Trastuzumab	57 (39.6)	103 (52.0)
T-DXd	12 (8.3)	64 (32.3)
T-DM1	75 (52.1)	26 (13.1)
Pertuzumab	17 (11.8)	31 (15.7)
Taxane	22 (15.3)	38 (19.2)
Taxane and trastuzumab	12 (8.3)	33 (16.7)
Other HER2-directed therapy	57 (39.6)	102 (51.5)
HER2-directed TKI	52 (36.1)	95 (48.0)
Other HER2-directed antibody or ADC	13 (9.0)	23 (11.6)
Hormone therapy	29 (20.1)	41 (20.7)
Other systemic therapy	100 (69.4)	158 (79.8)

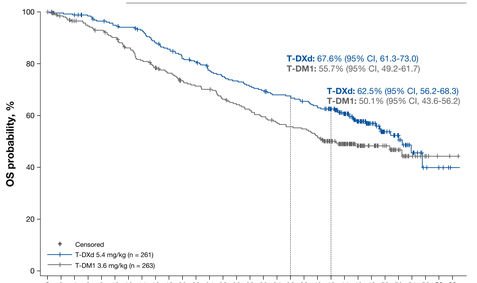
[a]The denominator for calculating the percentage was the number of patients who received at least 1 dose of study treatment (safety analysis set) in the T-DXd or the T-DM1 group.
[b]The denominator for calculating the percentage was the number of patients who discontinued study treatment in the T-DXd or the T-DM1 group.
[c]The denominator for calculating the percentage was the number of patients assigned to receive any anticancer systemic treatment in the T-DXd or the T-DM1 group. Patients could have received more than 1 type of therapy.

Overall Survival

- At the current DCO, 236 OS events (110 in the T-DXd group and 126 in the T-DM1 group) were observed (**Figure 4**)
  - Median OS was 52.6 months for T-DXd and 42.7 months for T-DM1

Figure 4. Overall Survival

	T-DXd n = 261	T-DM1 n = 263
Median (95% CI), months	52.6 (48.7-NE)	42.7 (35.4-NE)
HR (95% CI)	0.73 (0.56-0.94)	
Patients with events, n (%)	110 (42.1)	126 (47.9)

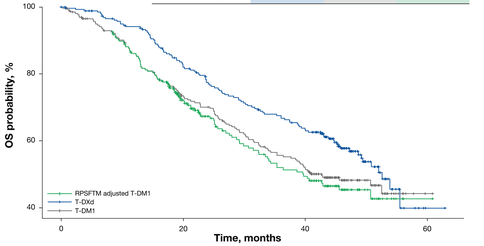


No. of patients still at risk
T-DXd 5.4 mg/kg (n = 261): 261 257 255 250 244 239 236 231 219 212 202 198 188 182 178 173 169 163 162 156 151 143 115 91 60 40 32 15 6 4 1
T-DM1 3.6 mg/kg (n = 263): 263 253 244 238 233 225 213 201 193 185 175 170 167 157 151 146 140 134 130 128 121 100 85 63 45 33 21 10 5 2 1

- Sensitivity analysis was conducted on the OS of the T-DM1 group using a rank-preserving structure failure time model (RPSFTM) to adjust the OS for patients who received post-trial T-DXd treatment (**Figure 5**)
  - Median OS adjusted by the RPSFTM was 39.8 months
  - The HR for OS between the T-DXd group and the RPSFTM adjusted T-DM1 group was 0.66 (95% CI, 0.51-0.87)

Figure 5. Sensitivity Analysis: OS in the T-DM1 Group Adjusted for Post-Trial T-DXd Treatment

	T-DXd n = 261	T-DM1 n = 263	T-DM1 n = 263 (adjusted)
Median, months (95% CI)	52.6 (48.7-NE)	42.7 (35.4-NE)	39.8 (32.4-NE)



Safety

- Median treatment duration was 18.2 months (range, 0.7-56.6 months) for T-DXd and 6.9 months (range, 0.7-55.2 months) for T-DM1
- Any-grade drug-related treatment emergent adverse events (TEAEs) were reported in 252 patients (98.1%) treated with T-DXd and 228 patients (87.4%) treated with T-DM1 (**Table 2**)
- The most common TEAEs reported with T-DXd treatment included nausea (77.0%), fatigue (53.3%), and vomiting (52.9%), whereas the most common TEAEs reported with T-DM1 treatment included thrombocytopenia (55.9%), transaminases increased (47.5%), and fatigue (35.2%)
- Exposure-adjusted incidence rates (EAIRs), which account for differences between treatment durations, were lower with T-DXd than with T-DM1 for any-grade TEAEs (0.53 vs 1.10), grade ≥3 TEAEs (0.31 vs 0.60), and serious TEAEs (0.15 vs 0.26), respectively

Table 2. Overall Safety Summary

n (%)	T-DXd n = 257[a]	T-DM1 n = 261[a]
Any drug-related TEAEs	252 (98.1)	228 (87.4)
Drug-related grade ≥3 TEAEs	125 (48.6)	111 (42.5)
Serious drug-related TEAEs	35 (13.6)	20 (7.7)
Drug-related TEAEs associated with drug interruption	113 (44.0)	48 (18.4)
Drug-related TEAEs associated with dose reduction	72 (28.0)	40 (15.3)
Drug-related TEAEs associated with discontinuation	58 (22.6)	19 (7.3)
Drug-related TEAEs associated with an outcome of death	0	0

[a]Includes all randomized patients who received at least 1 dose of study treatment.

- With additional follow-up since the previous analysis,[2] 4 new events of adjudicated drug-related ILD/pneumonitis (all grade 2) occurred in the T-DXd group (**Table 3**)
  - Outcomes of those 4 patients: not recovered/not resolved (n = 1), recovered/resolved with sequelae (n = 2), recovered/resolved (n = 1)
- In the T-DM1 group, there was 1 additional grade 1 event of ILD/pneumonitis since the previous data cutoff[2]
- As previously reported,[2] only 2 patients experienced grade 3 adjudicated drug-related ILD/pneumonitis events in the T-DXd group (both events resolved); no grade 4 or 5 events were observed
- Consistent with a previous study,[5] most ILD/pneumonitis events occurred within the first year of T-DXd treatment (**Table 3**)
- EAIRs for ILD/pneumonitis were 0.09 with T-DXd and 0.04 with T-DM1

Table 3. Adjudicated Drug-Related ILD/Pneumonitis

Adjudicated drug-related ILD/pneumonitis events for the entire study period through November 20, 2023 (DCO)						
n (%)[a]	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any grade**
T-DXd (n = 257)[b]	11 (4.3)	30 (11.7)	2 (0.8)	0	0	43 (16.7)
T-DM1 (n = 261)[b]	5 (1.9)	3 (1.1)	1 (0.4)	0	0	9 (3.4)
Time to first adjudicated drug-related ILD/pneumonitis[c] in the T-DXd group by CTCAE grade at the time of diagnosis						
≤6 months	3 (1.1)	10 (3.8)	1 (0.4)	0	0	14 (5.4)
>6 to ≤12 months	5 (1.9)	7 (2.7)	0	0	0	12 (4.6)
>12 to ≤24 months	5 (1.9)	5 (1.9)	1 (0.4)	0	0	11 (4.2)
>24 months	1 (0.4)	5 (1.9)	0	0	0	6 (2.3)

[a]Grade is based on the worst CTCAE grade within the same AE/ILD event.
[b]Includes all randomized patients who received at least 1 dose of study treatment.
[c]Time to first adjudicated ILD onset (months) = (onset date of first ILD adjudicated as drug-related – first dose date + 1)/365.25×12.

DESTINY-Breast03

DESTINY-Breast07: dose-expansion analysis of T-DXd monotherapy and T-DXd + pertuzumab in patients with previously untreated HER2+ mBC

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On behalf of the DESTINY-Breast07 investigators

DESTINY-Breast07: key takeaways

This is the first dataset of T-DXd monotherapy and T-DXd + pertuzumab as first-line treatment for HER2+ mBC

- The data showed robust efficacy in terms of **ORR, median DOR, and PFS rate at 12 months**
- There are **62.7%** and **56.0%** of patients receiving **ongoing study treatment**, with a **median duration of follow up** of **23.9 months** and **25.3 months**, in the T-DXd monotherapy and T-DXd + pertuzumab modules, respectively
- Encouraging clinical activity was observed with T-DXd monotherapy and T-DXd + pertuzumab in first-line HER2+ mBC, irrespective of disease status and HR status
- The **safety profiles** of T-DXd and pertuzumab were **consistent** with their individual known profiles
  - There were **no ILD/pneumonitis-related deaths** in either module

DOR, duration of response; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; ILD, interstitial lung disease; mBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

Study background and rationale

- HER2+ breast cancer occurs in up to approximately 20% of primary breast cancers[1,2]
- The current first-line therapy for HER2+ mBC is THP based on the CLEOPATRA study, which reported a median PFS of 18.7 months[3,4]
- T-DXd monotherapy has demonstrated impressive efficacy in HER2+ mBC and is approved for adult patients with HER2+ advanced/mBC progressing after trastuzumab and taxanes, based on the results from DESTINY-Breast03[5–8]
- DESTINY-Breast07 is a Phase 1b/2, multicenter, open-label, modular study exploring the safety, tolerability, and antitumor activity of T-DXd alone or in combination with other anticancer agents in patients with HER2+ mBC who have received no prior therapy in the metastatic setting (NCT04538742; Part 2, Modules 0–5)
- These results are from an interim analysis of the dose-expansion phase, assessing T-DXd alone and in combination with pertuzumab as first-line treatment in HER2+ mBC

HER2+, human epidermal growth factor receptor 2–positive; mBC, metastatic breast cancer; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; THP, taxane, trastuzumab, and pertuzumab

1. Wolff AC, et al. *J Clin Oncol*. 2013;31:3997–4013; 2. Morales S, et al. *Cancers (Basel)*. 2021;13:5771; 3. Giordano SH, et al. *J Clin Oncol*. 2022;40:2612–2635; 4. Swain SM, et al. *Lancet Oncol*. 2020;21:519–530; 5. Modi S, et al. *N Engl J Med*. 2020;382:610–621; 6. Cortés J, et al. *N Engl J Med*. 2022;386:1143–1154; 7. André F, et al. *Lancet*. 2023;401:1773–1785; 8. Enhertu (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information. 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s021lbl.pdf (Accessed March 18, 2024)

Study design

DESTINY-Breast07: a Phase 1b/2, multicenter, open-label, two-part, modular study (NCT04538742)

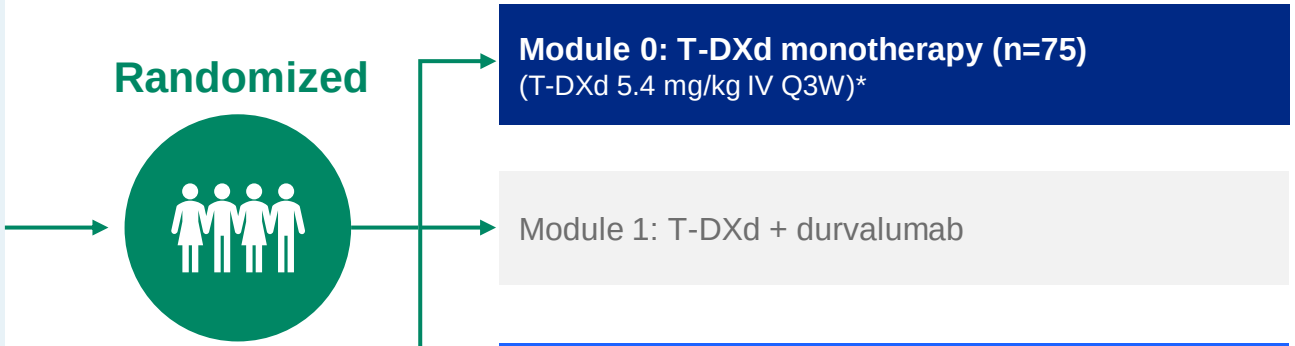
PATIENT POPULATION

- Locally assessed HER2+ (IHC 3+, IHC 2+/ISH+) advanced/mBC, with measurable disease per RECIST 1.1
- Either no brain metastases or previously treated stable brain metastases
- ECOG PS of 0 or 1

Prior lines of therapy

- No prior therapy for mBC was allowed
- A disease-free interval of ≥12 months from adjuvant HER2-directed therapy or chemotherapy was required
- Prior taxane, trastuzumab, and pertuzumab exposure was allowed in the (neo)adjuvant setting

This is the first dataset of T-DXd monotherapy and T-DXd + pertuzumab as first-line treatment for HER2+ mBC



Stratification factors

- HR status
- Disease status
- PD-L1 status

Endpoints for the Part 2 dose-expansion phase

Primary
Safety and tolerability, including AEs and SAEs

Key secondary
ORR, PFS (evaluated by investigator per RECIST 1.1), and DOR

DCO: December 22, 2023‡

Results reported here are from an interim analysis of the Part 2 dose-expansion phase for Modules 0 and 2 only; the Part 1 dose-finding phase of the study has been described previously[1]

*Patients in Module 0 received the approved T-DXd dose for HER2+ breast cancer; †patients received the RP2D from the study's dose-finding phase; ‡the corresponding abstract reported data from the August 1, 2023, DCO
AE, adverse event; DCO, data cutoff; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; IHC, immunohistochemistry; ISH+, in situ hybridization–positive; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RP2D, recommended Phase 2 dose; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

1. André F, et al. Poster presented at ASCO 2022 (Abstract 3025)

Baseline characteristics

	T-DXd monotherapy (n=75)	T-DXd + pertuzumab (n=50)
Median age, years (range)	57.0 (33.0–80.0)	56.5 (24.0–75.0)
Female, n (%)	74 (98.7)*	50 (100)
Race, n (%)		
White	52 (69.3)	37 (74.0)
Asian	20 (26.7)	12 (24.0)
Black or African American	2 (2.7)	0
Not reported	1 (1.3)	0
Other	0	1 (2.0)
HER2 status, n (%)		
IHC 3+[†]	60 (80.0)	41 (82.0)
IHC 2+/ISH+	14 (18.7)	9 (18.0)
IHC 2+	1 (1.3)	0
HR status, n (%)		
Positive[‡]	47 (62.7)	34 (68.0)
Negative	28 (37.3)	16 (32.0)
Disease status, n (%)		
Recurrent[§]	27 (36.0)	20 (40.0)
De novo[¶]	48 (64.0)	30 (60.0)
ECOG PS, n (%)		
0	49 (65.3)	37 (74.0)
1	26 (34.7)	13 (26.0)

Prior HER2-directed therapy in patients with recurrent mBC

n (%)	T-DXd monotherapy (n=27)	T-DXd + pertuzumab (n=20)
Trastuzumab	14 (51.9)	13 (65.0)
Pertuzumab	4 (14.8)	2 (10.0)
T-DM1	2 (7.4)	0

DCO was December 22, 2023

*Male, n=1; [†]regardless of ISH status; [‡]defined as ER- and/or PR-positive (ER or PR ≥1%); [§]defined as previously treated in the (neo)adjuvant setting with chemotherapy, HER2-directed agents, or endocrine therapy and includes previously treated HER2-negative patients who now have HER2-positive disease in the metastatic setting; [¶]defined as no prior systemic therapy in the (neo)adjuvant setting with chemotherapy, HER2-directed agents, or endocrine therapy

DCO, data cutoff; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; ISH+, in situ hybridization–positive; mBC, metastatic breast cancer; PR, progesterone receptor; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

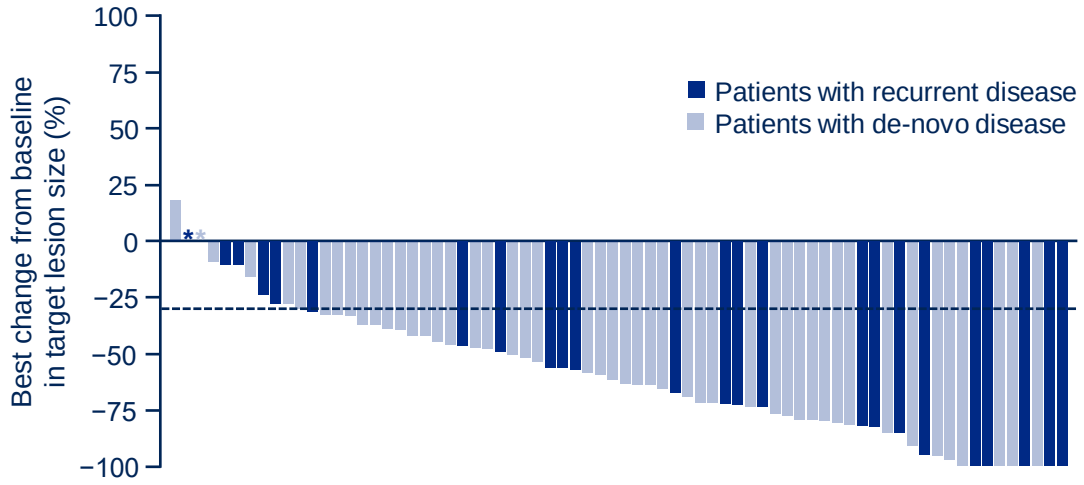
Patient disposition

	T-DXd monotherapy (n=75)	T-DXd + pertuzumab (n=50)
Median duration of follow up, months	23.9	25.3
Ongoing study treatment, n (%)	47 (62.7)	28 (56.0)
Discontinued treatment, n (%)	28 (37.3)	22 (44.0)
Objective disease progression	10 (13.3)	8 (16.0)
Adverse event	7 (9.3)	9 (18.0)
Withdrawal by patient	6 (8.0)	2 (4.0)
Other	5 (6.7)	3 (6.0)
Death*	2 (2.7)	1 (2.0)

DCO was December 22, 2023
*Includes death while on treatment with investigational product; investigators did not specifically record a reason for discontinuation of investigational product
DCO, data cutoff; T-DXd, trastuzumab deruxtecan

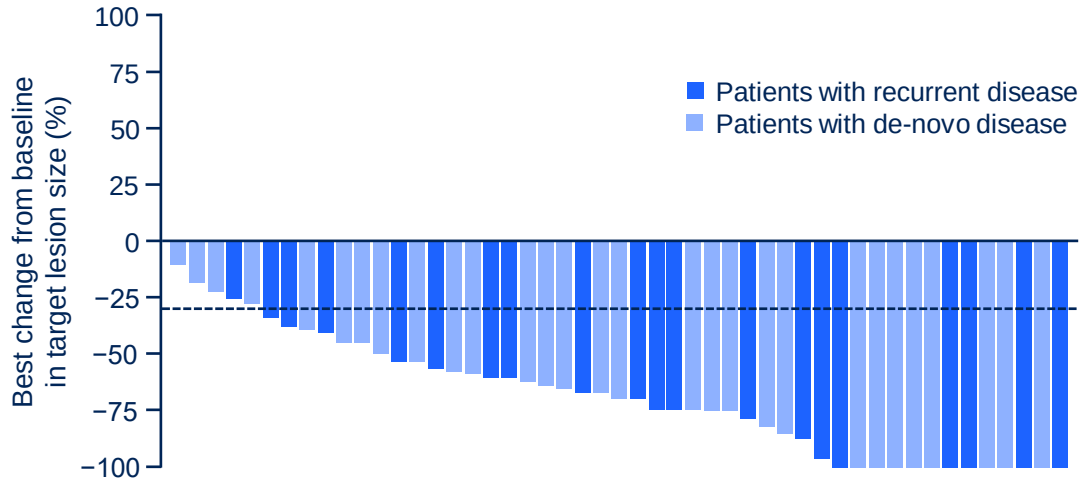
Response to treatment per RECIST 1.1 by investigator

T-DXd monotherapy (n=75)



Confirmed ORR, % (80% CI)	76.0 (68.5–82.4)
Complete response, n (%)	6 (8.0)
Partial response, n (%)	51 (68.0)
Median DOR, months (range)	NE (2.1–28.5)

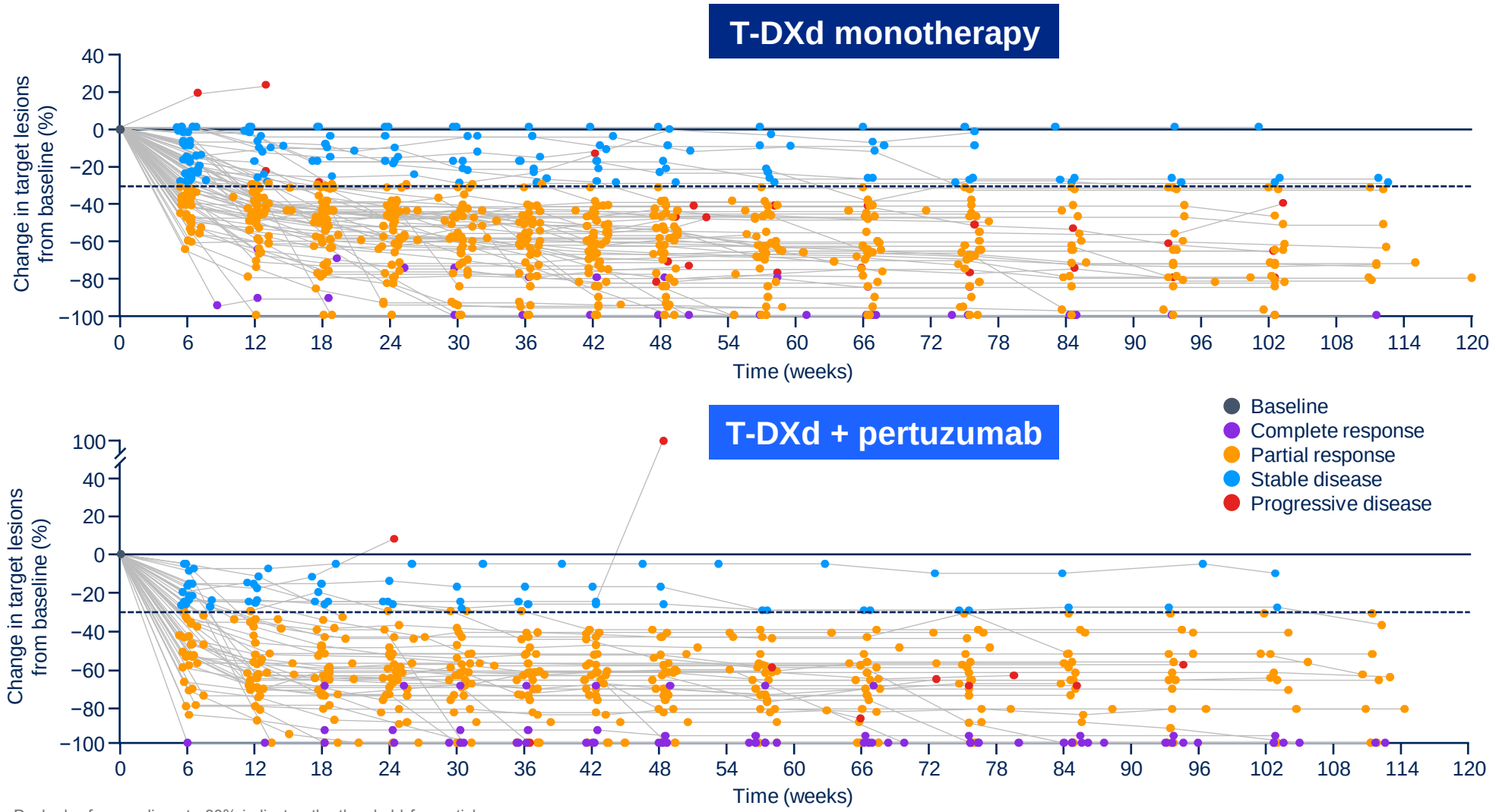
T-DXd + pertuzumab (n=50)



Confirmed ORR, % (80% CI)	84.0 (75.3–90.5)
Complete response, n (%)	10 (20.0)
Partial response, n (%)	32 (64.0)
Median DOR, months (range)	NE (4.5–28.3)

Dashed reference line at −30% indicates the threshold for partial response
Responses are captured for patients with baseline data and at least one follow-up assessment
DCO was December 22, 2023. Median duration of follow up was 23.9 months for T-DXd monotherapy and 25.3 months for T-DXd + pertuzumab
*Patients had 0% change from baseline
CI, confidence interval; DCO, data cutoff; DOR, duration of response; NE, not evaluable; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

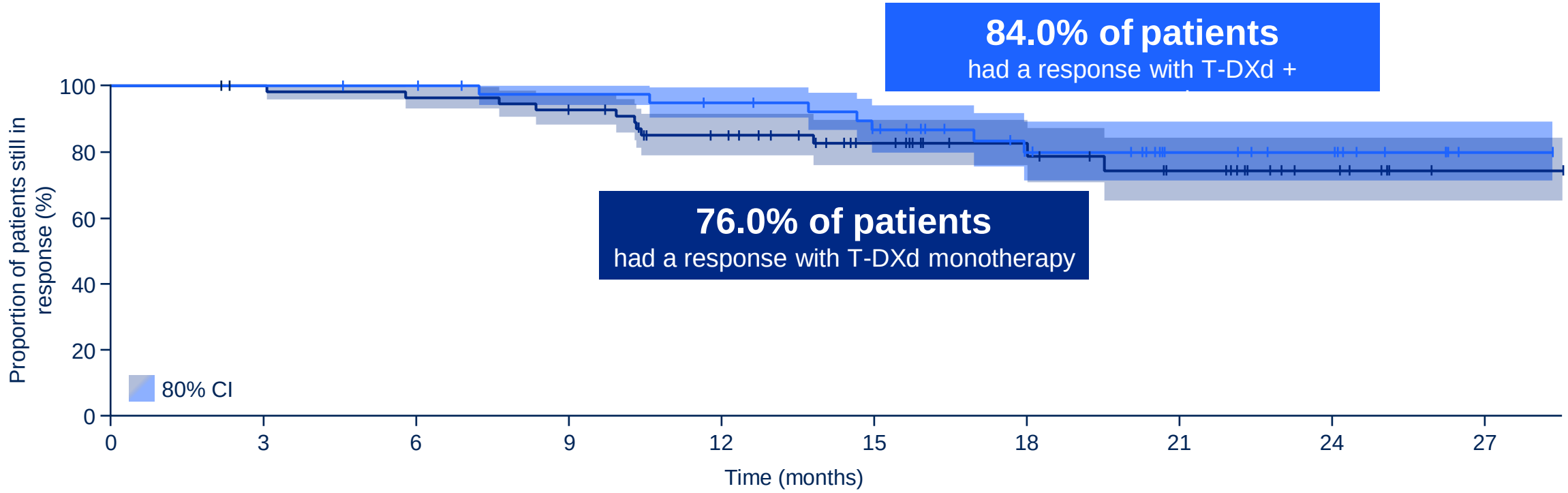
Percentage change in target lesion size from baseline



The majority of responses were observed by the 12-week scan and were durable

Dashed reference line at −30% indicates the threshold for partial response
DCO was December 22, 2023. Median duration of follow up was 23.9 months for T-DXd monotherapy and 25.3 months for T-DXd + pertuzumab. DCO, data cutoff; T-DXd, trastuzumab deruxtecan

Duration of response



Number at risk

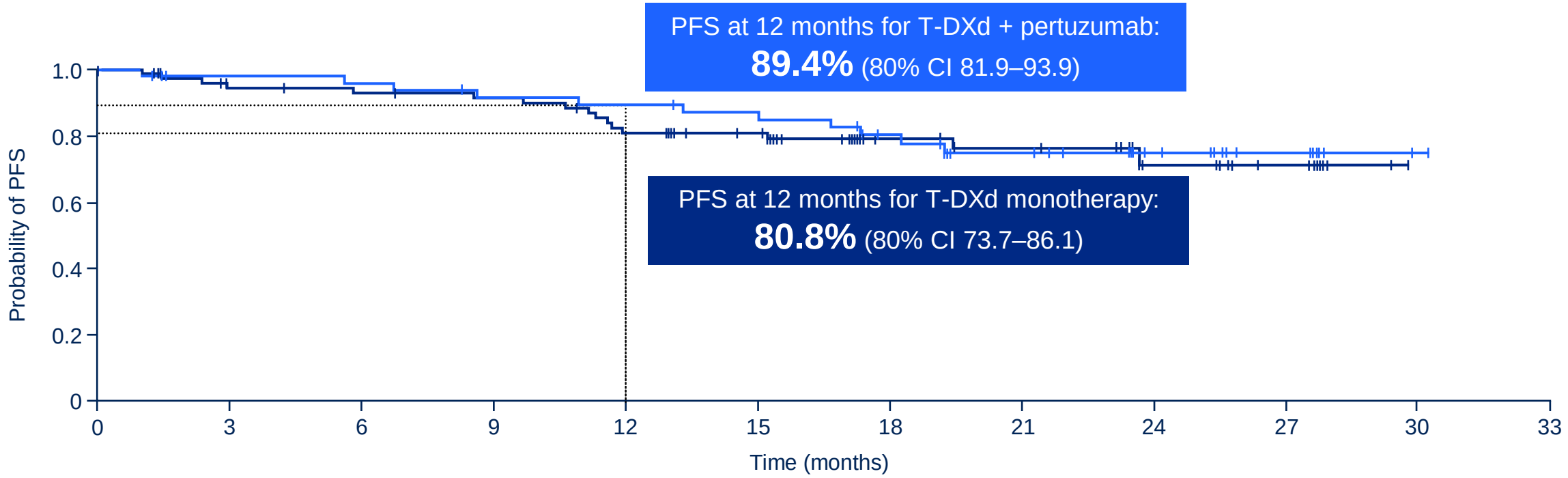
T-DXd monotherapy	57	55	53	50	41	28	21	15	7	1
T-DXd + pertuzumab	42	42	41	38	36	31	21	13	10	1

Number of randomized patients / number of events

T-DXd monotherapy	75 / 11
T-DXd + pertuzumab	50 / 7

DCO was December 22, 2023. Median duration of follow up was 23.9 months for T-DXd monotherapy and 25.3 months for T-DXd + pertuzumab
CI, confidence interval; DCO, data cutoff; T-DXd, trastuzumab deruxtecan

Progression-free survival



Number at risk

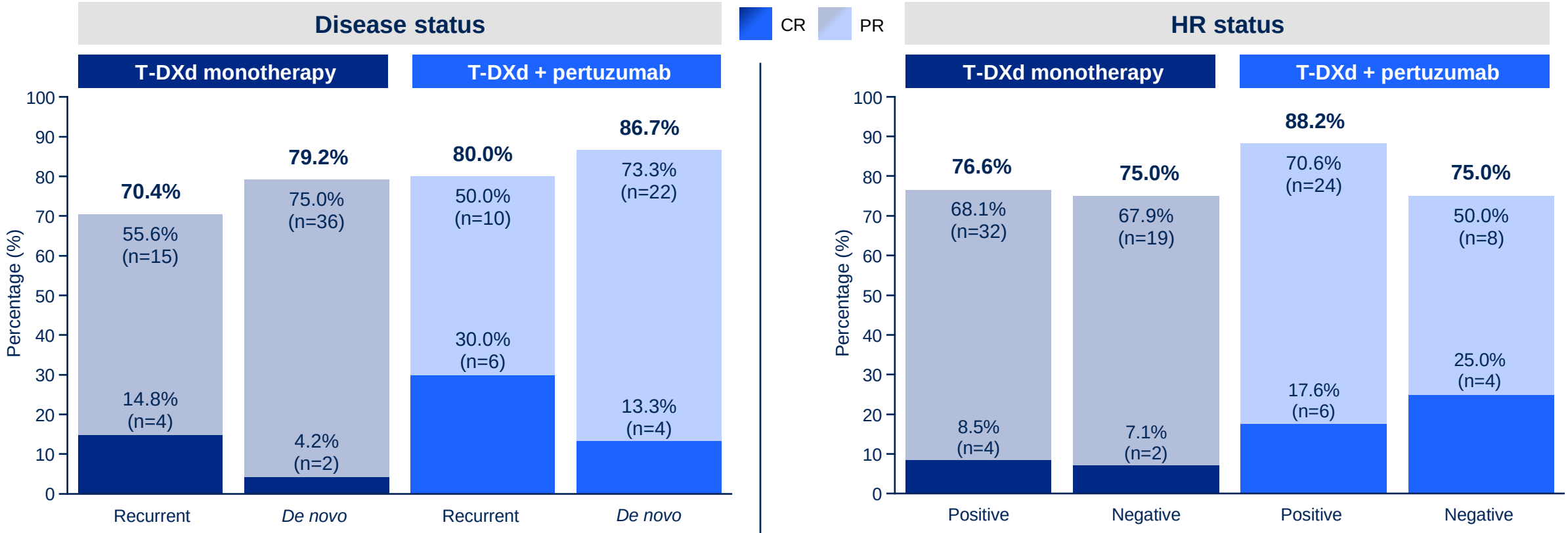
T-DXd monotherapy	75	65	63	61	53	47	27	24	13	8	0	0
T-DXd + pertuzumab	50	46	45	42	41	38	31	23	13	7	1	0

Number of randomized patients / number of events

T-DXd monotherapy	75 / 16
T-DXd + pertuzumab	50 / 11

The number of PFS events is small, and most patients were censored
DCO was December 22, 2023. Median duration of follow up was 23.9 months for T-DXd monotherapy and 25.3 months for T-DXd + pertuzumab
CI, confidence interval; DCO, data cutoff; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

cORR and BOR by subgroup per RECIST 1.1 by investigator



	Recurrent	*De novo*	Recurrent	*De novo*
Patients, n	27	48	20	30
cORR, n (%)	19 (70.4)	38 (79.2)	16 (80.0)	26 (86.7)
80% CI	56.4–81.9	69.7–86.6	63.9–91.0	75.1–94.1
SD, n (%)	6 (22.2)	8 (16.7)	4 (20.0)	3 (10.0)
PD, n (%)	1 (3.7)	2 (4.2)	0	1 (3.3)
NE, n (%)	1 (3.7)	0	0	0

	Positive	Negative	Positive	Negative
Patients, n	47	28	34	16
cORR, n (%)	36 (76.6)	21 (75.0)	30 (88.2)	12 (75.0)
80% CI	66.8–84.5	61.5–85.5	77.9–94.8	56.1–88.6
SD, n (%)	9 (19.1)	5 (17.9)	4 (11.8)	3 (18.8)
PD, n (%)	2 (4.3)	1 (3.6)	0	1 (6.3)
NE, n (%)	0	1 (3.6)	0	0

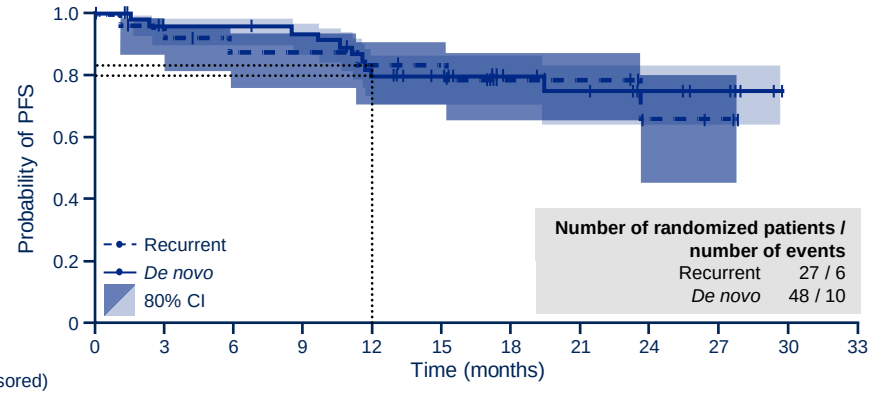
DCO was December 22, 2023

BOR, best overall response; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DCO, data cutoff; HR, hormone receptor; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; T-DXd, trastuzumab deruxtecan

Progression-free survival by subgroup

Disease status

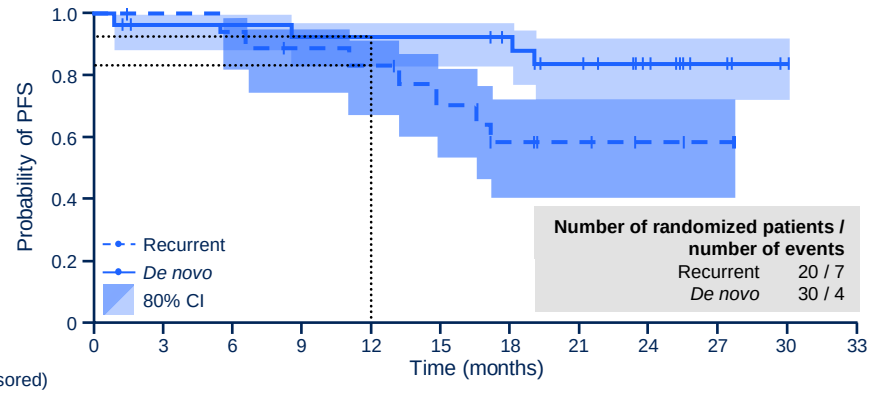
T-DXd monotherapy



Number at risk (censored)

Recurrent	27 (0)	22 (3)	20 (4)	20 (4)	19 (4)	18 (5)	10 (12)	9 (13)	3 (18)	2 (19)	0 (21)	0 (21)
De novo	48 (0)	43 (3)	43 (3)	41 (4)	34 (5)	29 (10)	17 (22)	15 (23)	10 (28)	6 (32)	0 (38)	0 (38)

T-DXd + pertuzumab

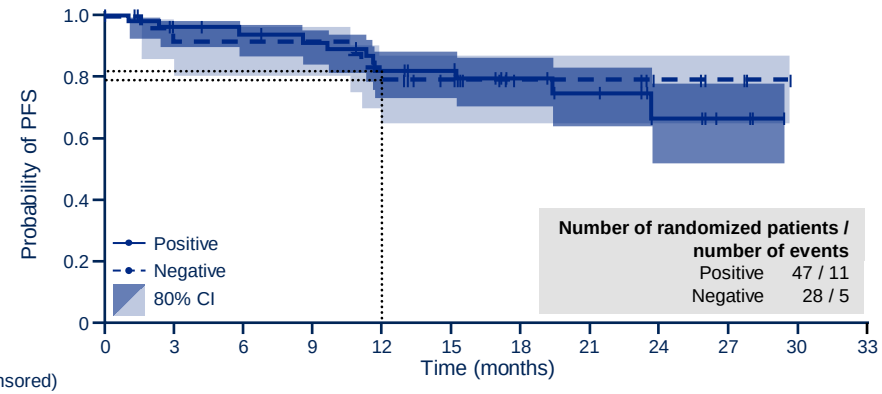


Number at risk (censored)

Recurrent	20 (0)	19 (1)	18 (1)	16 (2)	15 (2)	12 (3)	8 (5)	5 (8)	3 (10)	2 (11)	0 (13)	0 (13)
De novo	30 (0)	27 (2)	27 (2)	26 (2)	26 (2)	26 (2)	23 (5)	18 (8)	10 (16)	5 (21)	1 (25)	0 (26)

HR status

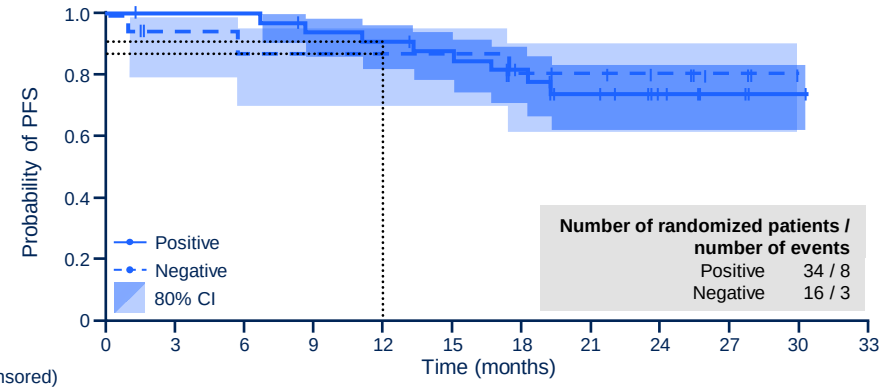
T-DXd monotherapy



Number at risk (censored)

Positive	47 (0)	44 (1)	42 (2)	40 (3)	35 (4)	33 (6)	18 (20)	15 (22)	7 (29)	4 (32)	0 (36)	0 (36)
Negative	28 (0)	21 (5)	21 (5)	21 (5)	18 (5)	14 (9)	9 (14)	9 (14)	6 (17)	4 (19)	0 (23)	0 (23)

T-DXd + pertuzumab



Number at risk (censored)

Positive	34 (0)	33 (1)	33 (1)	30 (2)	29 (2)	26 (3)	22 (6)	15 (11)	7 (19)	4 (22)	1 (25)	0 (26)
Negative	16 (0)	13 (2)	12 (2)	12 (2)	12 (2)	12 (2)	9 (4)	8 (5)	6 (7)	3 (10)	0 (13)	0 (13)

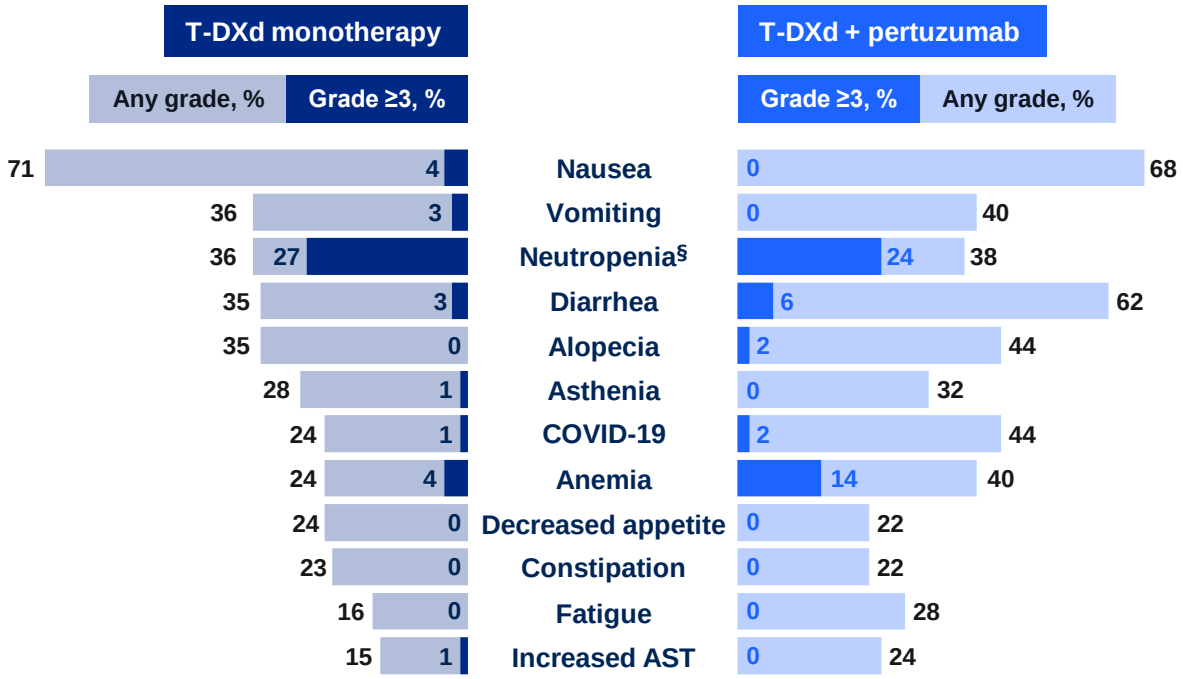
The number of PFS events is small, and most patients were censored

DCO was December 22, 2023. CI, confidence interval; DCO, data cutoff; HR, hormone receptor; PFS, progression-free survival, T-DXd, trastuzumab deruxtecan

Safety overview

	T-DXd monotherapy (n=75)	T-DXd + pertuzumab (n=50)
Median actual treatment duration, months (range)*		
T-DXd	16.3 (0.7–30.9)	17.8 (0.9–30.7)
Pertuzumab	N/A	17.6 (0.9–30.7)
Any AE, n (%)	75 (100)	50 (100)
Any AEs Grade ≥3, n (%)	39 (52.0)	31 (62.0)
AEs associated with drug interruptions of T-DXd, n (%)	44 (58.7)	32 (64.0)
AEs associated with dose reduction of T-DXd, n (%)	12 (16.0)	8 (16.0)
AEs associated with discontinuation of T-DXd, n (%)†	8 (10.7)	8 (16.0)
Any SAEs, n (%)	13 (17.3)	13 (26.0)
AEs leading to death, n (%)	1 (1.3)‡	0
AESIs, n (%)		
Pneumonitis (adjudicated as ILD related to T-DXd)	7 (9.3)	7 (14.0)
Grade 1	2 (2.7)	0
Grade 2	5 (6.7)	6 (12.0)
Grade 3	0	1 (2.0)
LV dysfunction (possibly related to T-DXd)	5 (6.7)	2 (4.0)

Any-grade AEs (>20% of patients in either module) with incidence of Grade ≥3 events



Grade 2 diarrhea events were reported in:
- **13.3%** of patients in the **T-DXd monotherapy** module
- **32.0%** of patients in the **T-DXd + pertuzumab** module

DCO was December 22, 2023

*Total treatment duration, excluding dose delays; †discontinuation of T-DXd due to toxicities resulted in the discontinuation of pertuzumab until resolved; ‡reported by investigator as non-treatment-related post-acute COVID-19 syndrome; §grouped term including neutropenia, decreased neutrophil count, and febrile neutropenia events

AE, adverse event; AESI, adverse event of special interest; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; DCO, data cutoff; ILD, interstitial lung disease; LV, left ventricular; N/A, not applicable; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

Conclusions (1/2)

- This is the **first dataset** of **T-DXd monotherapy** and **T-DXd + pertuzumab** as **first-line treatment** for **HER2+ mBC**
- T-DXd monotherapy (n=75) and T-DXd + pertuzumab (n=50) showed robust efficacy:
  - **Confirmed ORR** was **76.0%** and **84.0%** for T-DXd monotherapy and T-DXd + pertuzumab, respectively
  - **Median DOR** was **not reached** for T-DXd monotherapy or T-DXd + pertuzumab
  - **PFS rate at 12 months** was **80.8%** and **89.4%** for T-DXd monotherapy and T-DXd + pertuzumab, respectively; the number of PFS events was small and most patients were censored
- There are **62.7%** and **56.0%** of patients receiving **ongoing study treatment**, with a **median duration of follow up** of **23.9 months** and **25.3 months**, in the T-DXd monotherapy and T-DXd + pertuzumab modules, respectively
- Encouraging clinical activity was observed with T-DXd monotherapy and T-DXd + pertuzumab in first-line HER2+ mBC, irrespective of disease status and HR status

DOR, duration of response; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; mBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

Conclusions (2/2)

- The **safety profiles** of T-DXd and pertuzumab were **consistent** with their individual known profiles
  - The incidence of **ILD/pneumonitis events** was **9.3%** and **14.0%** in the T-DXd monotherapy and T-DXd + pertuzumab modules, respectively; there were **no ILD/pneumonitis-related deaths** in either module
- T-DXd monotherapy and T-DXd + pertuzumab are being evaluated versus THP, in patients with HER2+ mBC in the first-line setting, in the Phase 3 DESTINY-Breast09 clinical trial

HER2+, human epidermal growth factor receptor 2–positive; ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; THP, taxane, trastuzumab, and pertuzumab

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Trastuzumab Deruxtecan in Patients With *HER2*-Mutant Metastatic Non–Small Cell Lung Cancer: Final Analysis Results of DESTINY-Lung02

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Objective

- This final analysis reports updated efficacy and safety results of DESTINY-Lung02, which was conducted to investigate trastuzumab deruxtecan (T-DXd) 5.4 mg/kg and 6.4 mg/kg in patients with previously treated human epidermal growth factor receptor 2 (*HER2*; *ERBB2*)–mutant (*HER2*m) metastatic non–small cell lung cancer (mNSCLC). We also report data on clinically relevant subgroups and patient-reported outcomes (PROs)

Conclusions

- In this final analysis, T-DXd 5.4 mg/kg and 6.4 mg/kg continued to show strong and durable responses in patients with previously treated *HER2*m mNSCLC, consistent with the primary analysis
  - Responses were observed in both treatment arms regardless of the number of prior systemic anticancer therapies and baseline central nervous system (CNS) metastases
- The safety profiles of both T-DXd doses were acceptable and generally manageable, and no significant changes in toxicity were observed with longer follow-up
- Health-related quality of life (HRQoL) was maintained for the duration of T-DXd treatment while sample size was considered meaningful for analysis, with no detrimental impact on HRQoL observed at either dose
- Overall, the approved T-DXd 5.4 mg/kg dose was associated with a more favorable benefit/risk profile and a reduced incidence of adjudicated drug-related interstitial lung disease (ILD)/pneumonitis, reinforcing the use of T-DXd in this patient population

Plain Language Summary

Why did we perform this research?
Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate designed to target and kill cancer cells that express the human epidermal growth factor receptor 2 (HER2) protein. It is the only approved HER2-directed treatment for patients with previously treated *HER2* (*ERBB2*)-mutant metastatic non–small cell lung cancer (mNSCLC).[1-3] The DESTINY-Lung02 study was designed to determine the efficacy and safety of 2 T-DXd doses (5.4 mg/kg and 6.4 mg/kg) in these patients.[3] In the primary analysis of the study, T-DXd 5.4 mg/kg and 6.4 mg/kg showed strong and durable responses and acceptable and generally manageable safety profiles.[3] The objective of this final analysis was to assess the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg after extended follow-up of patients participating in the DESTINY-Lung02 trial, as well as patient-reported outcomes (PROs)

How did we perform this research?
In the DESTINY-Lung02 study, 152 patients were randomly assigned 2:1 to receive T-DXd 5.4 mg/kg (n = 102) or T-DXd 6.4 mg/kg (n = 50). T-DXd efficacy, safety, and PROs were evaluated in each group

What were the findings of this research?
Consistent with results of the primary analysis, findings from the final analysis of DESTINY-Lung02 showed that both T-DXd doses continued to demonstrate strong and durable antitumor activity in patients with previously treated *HER2*-mutant mNSCLC. This was true regardless of central nervous system metastasis at baseline or prior cancer treatment received. Additionally, although both T-DXd doses had acceptable and generally manageable safety profiles with longer follow-up, the 5.4 mg/kg dose had a more favorable profile considering the benefits and risks of the treatment as a whole. Finally, we found that T-DXd had no detrimental impact on patient quality of life for the duration of treatment

What were the implications of this research?
After extended follow-up, the strong and durable antitumor activity of the approved 5.4 mg/kg dose of T-DXd, together with its more favorable benefit/risk profile and non-detrimental impact on patient quality of life, continues to reinforce the use of T-DXd for patients with *HER2*-mutant mNSCLC

Where can I access more information?
For more detailed information on the DESTINY-Lung02 study and its outcomes, you can visit https://clinicaltrials.gov/ct2/show/NCT04644237

References

1. Nakada T et al. *Chem Pharm Bull*. 2019;67(3):173-185.
2. Ogitani Y et al. *Cancer Sci*. 2016;107(7):1039-1046.
3. Goto K et al. *J Clin Oncol*. 2023;41(31):4852-4863.

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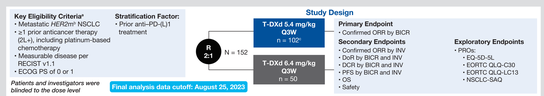
Introduction

- T-DXd is a HER2-directed antibody-drug conjugate and is the first and only HER2-directed therapy approved in several countries worldwide for patients with previously treated *HER2*m mNSCLC[1-6]
- In the primary analysis of DESTINY-Lung02 (NCT04644237; data cutoff: December 23, 2022), both T-DXd 5.4 mg/kg and 6.4 mg/kg demonstrated strong and durable responses and an acceptable and generally manageable safety profile in patients with previously treated *HER2*m mNSCLC[3]
  - The confirmed objective response rate (cORR) was 49.0% (95% CI, 39.0%-59.1%) and 56.0% (95% CI, 41.3%-70.0%) in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively[3]
  - T-DXd 5.4 mg/kg was associated with a more favorable benefit/risk profile due to the low rates of drug-related grade ≥3 treatment-emergent adverse events (TEAEs); drug-related TEAEs associated with discontinuation, reduction, or interruption; and adjudicated drug-related ILD/pneumonitis[3]

Methods

- DESTINY-Lung02 was a dose-blinded, randomized, multicenter, international, noncomparative, phase 2 trial in which patients with previously treated *HER2*m mNSCLC were randomly assigned 2:1 to receive T-DXd 5.4 mg/kg or 6.4 mg/kg once every 3 weeks (Q3W; **Figure 1**)
- At the final analysis data cutoff (August 25, 2023; additional 8 months of follow-up since the primary analysis data cutoff), the primary endpoint was cORR by blinded independent central review (BICR)
- Secondary endpoints included cORR by investigator assessment, duration of response (DoR) by BICR and investigator, progression-free survival (PFS) by BICR and investigator, overall survival (OS), and safety
- Exploratory endpoints included subgroup analysis and PROs
- Statistical hypothesis testing for the primary analysis was performed by comparing the lower limit of the 95% Clopper-Pearson CI of cORR with the benchmark ORR of 26.4%[3,7]
- This study was not powered to statistically compare between treatment arms

Figure 1. DESTINY-Lung02 Study Design



[a]Patients with stable brain metastases at baseline (asymptomatic; not requiring corticosteroid or anticonvulsant treatment) were eligible.
[b]Activating *HER2* mutation documented from an archival or fresh tumor tissue sample by certified local laboratory assessment.
[c]1 patient randomly assigned to the T-DXd 5.4 mg/kg arm did not receive treatment because the patient discontinued due to COVID-19 before cycle 1 day 1.

Results

Patient Disposition

- At the final analysis data cutoff (August 25, 2023), study treatment was ongoing in 12.9% of patients (13/101) in the T-DXd 5.4 mg/kg arm and 12.0% of patients (6/50) in the T-DXd 6.4 mg/kg arm

Baseline Characteristics

- Baseline demographics and clinical characteristics were similar across the T-DXd 5.4 mg/kg and 6.4 mg/kg arms (**Table 1**)
- In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively:
  - Most patients received prior anti–programmed death (ligand) 1 (PD-[L]1) therapy (73.5% and 78.0%)
  - Most patients had never smoked (53.9% and 58.0%)
  - *HER2* mutations were primarily in the kinase domain (97.1% and 100%)
  - Baseline CNS metastasis was present in 34.3% and 44.0% of patients

Table 1. Demographics and Baseline Characteristics

Characteristics	T-DXd 5.4 mg/kg n = 102	T-DXd 6.4 mg/kg n = 50
Age, median (range), years	59.4 (31-84)	61.3 (28-86)
Female, n (%)	65 (63.7)	34 (68.0)
Region, n (%)		
Asia	63 (61.8)	30 (60.0)
Europe	33 (32.4)	17 (34.0)
North America	4 (3.9)	2 (4.0)
Other	2 (2.0)	1 (2.0)
ECOG PS at baseline, n (%)		
0	29 (28.4)	19 (38.0)
1	73 (71.6)	31 (62.0)
***HER2* mutation, n (%)**		
Kinase domain	99 (97.1)	50 (100)
Extracellular domain	3 (2.9)	0
CNS metastasis at baseline, n (%)	35 (34.3)	22 (44.0)
Smoking status, n (%)		
Never	55 (53.9)	29 (58.0)
Former	47 (46.1)	21 (42.0)
Renal function at baseline, n (%)		
Normal	38 (37.3)	16 (32.0)
Mild impairment	41 (40.2)	29 (58.0)
Moderate impairment	23 (22.5)	5 (10.0)
Prior lung resection, n (%)	22 (21.6)	12 (24.0)
Lines of prior systemic therapy for advanced/metastatic disease, n (%)		
≤2	69 (67.6)	31 (62.0)
>2	33 (32.4)	19 (38.0)
Prior anti–PD-(L)1 therapy, n (%)	75 (73.5)	39 (78.0)

Data cutoff: August 25, 2023.

Efficacy

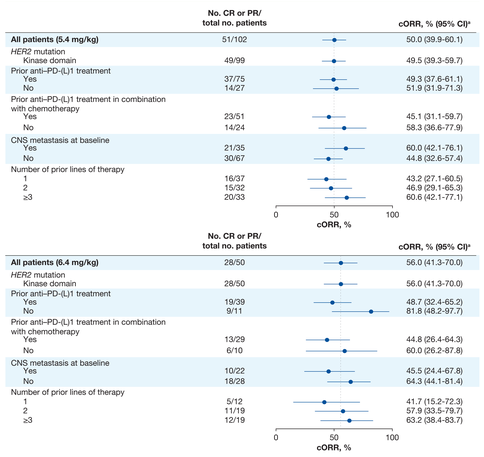
- At the final analysis data cutoff (August 25, 2023), the median duration of follow-up was 15.8 months (range, 1.1-28.6 months) and 16.5 months (range, 0.6-28.7 months) in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively
- cORR by BICR was 50.0% (95% CI, 39.0%-60.1%) with T-DXd 5.4 mg/kg and 56.0% (95% CI, 41.3%-70.0%) with T-DXd 6.4 mg/kg, consistent with the primary analysis (**Table 2**)
  - Consistent with the primary analysis, responses were observed across treatment arms regardless of the number of prior systemic anticancer therapies the patients had received and presence or absence of baseline CNS metastases (**Figure 2**)
- Median DoR by BICR was 12.6 months (95% CI, 6.4 months to not estimable [NE]) with T-DXd 5.4 mg/kg and 12.2 months (95% CI, 7.0 months to NE) with T-DXd 6.4 mg/kg (**Table 2**)

Table 2. Summary of Efficacy Results of T-DXd

	T-DXd 5.4 mg/kg n = 102	T-DXd 6.4 mg/kg n = 50
cORR,[a,b] n (% [95% CI])	51 (50.0 [39.9-60.1])	28 (56.0 [41.3-70.0])
CR	3 (2.9)	4 (8.0)
PR	48 (47.1)	24 (48.0)
SD	44 (43.1)	18 (36.0)
PD	4 (3.9)	2 (4.0)
Non-evaluable	3 (2.9)	2 (4.0)
DCR,[c] n (% [95% CI])	95 (93.1 [86.4-97.2])	46 (92.0 [80.8-97.8])
DoR,[b] median (95% CI), months	12.6 (6.4 to NE)	12.2 (7.0 to NE)

Data cutoff: August 25, 2023.
[a]Proportion of patients with confirmed CR or PR. [b]Assessed by BICR per RECIST v1.1. [c]Proportion of patients with confirmed CR, PR, or SD.

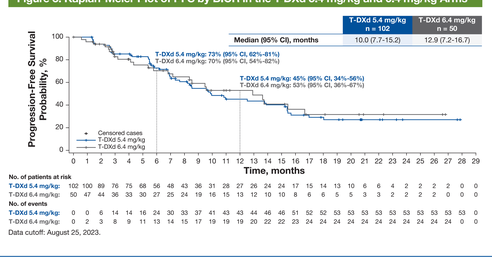
Figure 2. Subgroup Analysis of ORR by BICR



Data cutoff: August 25, 2023.
[a]ORR by BICR per RECIST v1.1. The 2-sided 95% CIs are based on the exact (Clopper-Pearson) binomial distribution.

- Median PFS by BICR was 10.0 months (95% CI, 7.7-15.2 months) with T-DXd 5.4 mg/kg and 12.9 months (95% CI, 7.2-16.7 months) with T-DXd 6.4 mg/kg (**Figure 3**)

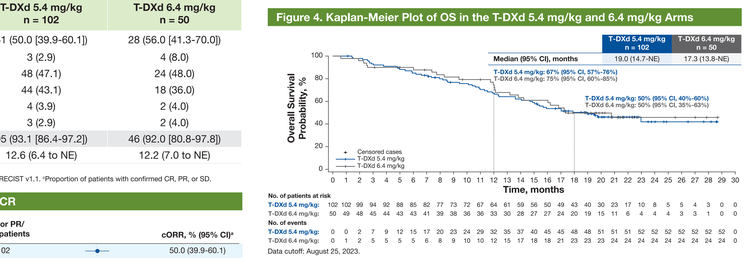
Figure 3. Kaplan-Meier Plot of PFS by BICR in the T-DXd 5.4 mg/kg and 6.4 mg/kg Arms



Data cutoff: August 25, 2023.

- Median OS was 19.0 months (95% CI, 14.7 months to NE) and 17.3 months (95% CI, 13.8 months to NE) with T-DXd 5.4 mg/kg and 6.4 mg/kg, respectively (**Figure 4**)

Figure 4. Kaplan-Meier Plot of OS in the T-DXd 5.4 mg/kg and 6.4 mg/kg Arms

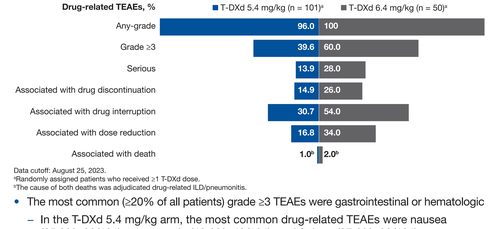


Data cutoff: August 25, 2023.

Safety

- Median treatment duration was 7.7 months (range, 0.7-27.6 months) with T-DXd 5.4 mg/kg and 8.3 months (range, 0.7-24.0 months) with T-DXd 6.4 mg/kg
- Drug-related grade ≥3 TEAEs were reported in 39.6% (40/101) and 60.0% (30/50) of patients in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively (**Figure 5**)
- Lower rates of drug-related TEAEs associated with discontinuation, reduction, and interruption were observed in the T-DXd 5.4 mg/kg arm, consistent with the primary analysis (**Figure 5**)

Figure 5. Overall Safety Summary of the T-DXd 5.4 mg/kg and 6.4 mg/kg Arms



Data cutoff: August 25, 2023.
[a]Randomly assigned patients who received ≥1 T-DXd dose.
[b]The cause of both deaths was adjudicated drug-related ILD/pneumonitis.

- The most common (≥20% of all patients) grade ≥3 TEAEs were gastrointestinal or hematologic
  - In the T-DXd 5.4 mg/kg arm, the most common drug-related TEAEs were nausea (65.3%; 66/101), neutropenia (42.6%; 43/101), and fatigue (37.6%; 38/101)
  - In the T-DXd 6.4 mg/kg arm, the most common drug-related TEAEs were nausea (78.0%; 39/50), neutropenia (56.0%; 28/50), fatigue (46.0%; 23/50), and decreased appetite (46.0%; 23/50)
  - The incidence of ≥3 grade hematologic events was lower among patients in the T-DXd 5.4 mg/kg arm than among patients in the 6.4 mg/kg arm (neutropenia [18.8% vs 38.0%], anemia [11.9% vs 16.0%], thrombocytopenia [5.9% vs 14.0%], and leukopenia [5.9% vs 16.0%], respectively)
- The rate of adjudicated drug-related ILD/pneumonitis was 14.9% (15/101) in the T-DXd 5.4 mg/kg arm and 32.0% (16/50) in the T-DXd 6.4 mg/kg arm (**Table 3**)
  - Most events were grade 1 or 2, with 1 grade 5 event occurring in each arm (1.0% and 2.0% in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively)
- In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively, adjudicated drug-related ILD/pneumonitis occurred in patients who received anti–PD-(L)1 treatment:
  - >3 months before receiving T-DXd (not including duration of previous treatment): 11.4% (5/44) and 35.7% (10/28)
  - ≤3 months before receiving T-DXd (not including duration of previous treatment): 20% (6/30) and 27.3% (3/11)
- In patients who did not previously receive anti–PD-(L)1 treatment, adjudicated drug-related ILD/pneumonitis occurred in 14.8% (4/27) and 27.3% (3/11) of patients in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively

Table 3. Adjudicated Drug-Related ILD/Pneumonitis Cases With T-DXd 5.4 mg/kg and 6.4 mg/kg

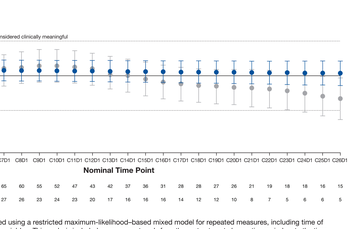
Adjudicated drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg n = 101[a]	T-DXd 6.4 mg/kg n = 50[a]
Total	15 (14.9)	16 (32.0)
Grade 1	4 (4.0)	3 (6.0)
Grade 2	9 (8.9)	11 (22.0)
Grade 3	1 (1.0)	1 (2.0)
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

Data cutoff: August 25, 2023.
[a]Randomly assigned patients who received ≥1 T-DXd dose.

Patient-Reported Outcomes

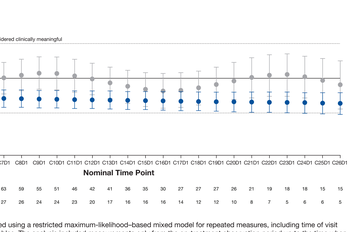
- In the T-DXd 5.4 mg/kg arm, overall HRQoL was sustained while on treatment, as suggested by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) global health status (GHS) score, which was maintained until cycle 26 (after which the number of patients remaining on treatment decreased to <10%, and the results were no longer informative) (**Figure 6**)
  - In the T-DXd 6.4 mg/kg arm, GHS scores were consistent with those of patients in the T-DXd 5.4 mg/kg arm
- EORTC QLQ-C30 pain and physical functioning scores, Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) pain symptom scores, and EuroQol 5-Dimension, 5-Level Cancer Specific Core Quality of Life Questionnaire (EQ-5D-5L) visual analog scale scores remained stable while on treatment with T-DXd 5.4 mg/kg and 6.4 mg/kg
- EORTC Lung Cancer Specific Quality of Life Questionnaire (QLQ-LC13) chest pain symptom scores were maintained for the duration of treatment with T-DXd 5.4 mg/kg and 6.4 mg/kg while sample size was considered informative (**Figure 7**)

Figure 6. EORTC QLQ-C30 GHS CFB[a] in the T-DXd 5.4 mg/kg and 6.4 mg/kg Arms



Data cutoff: August 25, 2023.
[a]LSM of CFB and 95% CI were calculated using a restricted maximum-likelihood–based mixed model for repeated measures, including time of visit and baseline score as independent variables. This analysis included measurements only from the on-treatment observation period up to the time when ≥10% of patients were still receiving study treatment.

Figure 7. EORTC QLQ-LC13 Chest Pain Symptoms CFB[a] in the T-DXd 5.4 mg/kg and 6.4 mg/kg Arms



Data cutoff: August 25, 2023.
[a]LSM of CFB and 95% CI were calculated using a restricted maximum-likelihood–based mixed model for repeated measures, including time of visit and baseline score as independent variables. This analysis included measurements only from the on-treatment observation period up to the time when ≥10% of patients were still receiving study treatment.

Abbreviations

2L+, second line of treatment or later; BICR, blinded independent central review; CFB, change from baseline; CNS, central nervous system; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13, European Organisation for the Research and Treatment of Cancer Lung Cancer Specific Quality of Life Questionnaire; EQ-5D-5L, EuroQol 5-Dimension, 5-Level Cancer Specific Core Quality of Life Questionnaire; GHS, global health status; HER2, human epidermal growth factor receptor 2; *HER2*m, human epidermal growth factor receptor 2–mutant; HRQoL, health-related quality of life; ILD, interstitial lung disease; INV, investigator assessment; LSM, least-squares mean; mNSCLC, metastatic non–small cell lung cancer; NE, not estimable; NSCLC, non–small cell lung cancer; NSCLC-SAQ, Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; Q3W, every 3 weeks; QoL, quality of life; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

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DESTINY-Lung02

Abstract # 8617

Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab with or without platinum chemotherapy as first-line therapy for advanced non-small cell lung cancer (NSCLC); subgroup analysis from TROPION-Lung02

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Objective

- Subgroup analysis of TROPION-Lung02 evaluating Dato-DXd + pembrolizumab ± platinum CT as 1L therapy for patients with advanced/metastatic NSCLC without actionable genomic alterations

Conclusions

- As a 1L therapy for advanced NSCLC, Dato-DXd + pembrolizumab ± platinum CT continues to demonstrate durable antitumor activity across all levels of PD-L1 expression and with both doublet and triplet regimens
  - In this non-randomized study, efficacy outcomes seen with the doublet regimen were not inferior to those seen with the triplet regimen
- Tolerability of the combinations was as expected based on known profiles of the individual agents, with no new safety signals observed
- To date, this is the largest dataset reported for any ADC combined with an anti–PD-1/-L1 agent in the 1L setting for advanced NSCLC
- These data support the evaluation of Dato-DXd + pembrolizumab ± CT vs standard of care therapies in the 1L setting in the pivotal phase 3 TROPION-Lung07 (NCT05555732) and TROPION-Lung08 (NCT05215340) studies

Background

- For patients with advanced/metastatic NSCLC, the standard first-line treatment is pembrolizumab monotherapy for those with high PD-L1 expression and pembrolizumab in combination with platinum-doublet CT for those with low PD-L1 expression; treatment outcomes when using PD-L1 inhibitors are worse in patients with low vs high PD-L1 expression[1]
- **Dato-DXd** is a **TROP2-directed antibody–drug conjugate (ADC)** composed of an anti-TROP2 mAb covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[2]
- Encouraging antitumor activity has been observed in patients with NSCLC receiving Dato-DXd in combination with IO (TROPION-Lung02[3] and TROPION-Lung04[4])
- TROPION-Lung02 (NCT04526691)[5] is the first study evaluating Dato-DXd + pembrolizumab ± platinum CT in advanced NSCLC without actionable genomic alterations
- Here, we report subgroup analyses from TROPION-Lung02 in patients receiving 1L therapy

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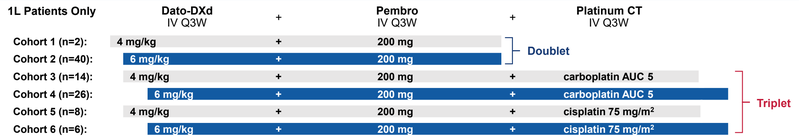
Methods

- TROPION-Lung02 is a phase 1b, multicenter, open-label study of Dato-DXd + pembrolizumab ± platinum CT in advanced NSCLC without actionable genomic alterations[a]
  - The safety of the Dato-DXd + pembrolizumab doublet was established prior to evaluation of the platinum-containing triplet
  - The safety of Dato-DXd 4-mg/kg combinations was established prior to evaluation of 6-mg/kg combinations
- Patients in the expansion stage were primarily treatment-naive

Key eligibility criteria

- **Advanced/metastatic NSCLC**
- **Dose escalation[b]:** ≤2 lines of prior therapy[c]
- **Dose expansion**
  - ≤1 line of platinum CT (cohorts 1 and 2)[c]
  - Treatment-naive (cohort 2; enrollment after June 30, 2022)[c]
  - Treatment-naive (cohorts 3–6)[c]



- **Primary objectives:** safety and tolerability
- **Secondary objectives:** efficacy, PK, and antidrug antibodies

Data cutoff: October 31, 2023.

[a]Patients with known actionable genomic alterations in *EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *RET*, or *MET*, or with alterations in other actionable oncogenic driver kinases were not eligible for this study. [b]The first 3 to 6 patients in each cohort were enrolled to confirm acceptable safety/DLT rate; the remaining patients are considered part of dose expansion (for which enrollment was ongoing at the time of data cutoff). [c]Prior therapy requirements are for treatment in the advanced/metastatic setting.

Results

Demographics and baseline characteristics of 1L patients

	Doublet (n=42)	Triplet (n=54)
Age, median (range), years	66 (49–83)	66 (35–80)
Male, n (%)	32 (76)	34 (63)
Asian race, n (%)	31 (74)	23 (43)
Histology, n (%)		
Adenocarcinoma	31 (74)	35 (65)
Squamous	9 (21)	12 (22)
Stage at study entry, n (%)		
IIIB	1 (2)	0
IIIC	0	1 (2)
IV	2 (5)	8 (15)
IVA	22 (52)	25 (46)
IVB	17 (41)	20 (37)
History of brain metastases, n (%)	4 (10)	10 (19)
ECOG PS 1, n (%)	24 (57)	33 (61)
PD-L1 expression[a], n (%)		
<1%	18 (43)	16 (30)
1–49%	19 (45)	23 (43)
≥50%	5 (12)	15 (28)

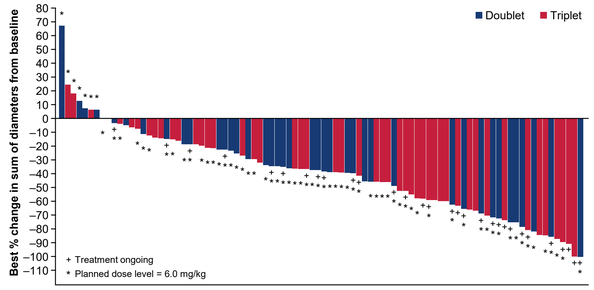
[a]Evaluated locally by tumor proportion score using immunohistochemistry (22C3 assay).

Efficacy outcomes in 1L patients, overall and by PD-L1 status[a,b]

	All 1L (n=96)		1L PD-L1 <1% (n=34)		1L PD-L1 1–49% (n=42)		1L PD-L1 ≥50% (n=20)	
	Doublet (n=42)	Triplet (n=54)	Doublet (n=18)	Triplet (n=16)	Doublet (n=19)	Triplet (n=23)	Doublet (n=5)	Triplet (n=15)
ORR, n (%)	22 (52)	30 (56)	8 (44)	5 (31)	9 (47)	17 (74)	5 (100)	8 (53)
[95% CI]	[36–68]	[41–69]	[22–69]	[11–59]	[24–71]	[52–90]	[48–100]	[27–79]
BOR, n (%)								
CR	1 (2)	1 (2)	1 (6)	0	0	1 (4)	0	0
PR	21 (50)	29 (54)	7 (39)	5 (31)	9 (47)	16 (70)	5 (100)	8 (53)
SD	15 (36)	18 (33)	8 (44)	10 (63)	7 (37)	3 (13)	0	5 (33)
PD	3 (7)	2 (4)	1 (6)	1 (6)	2 (11)	1 (4)	0	0
NE	2 (5)	4 (7)	1 (6)	0	1 (5)	2 (9)	0	2 (13)
DCR, n (%)	37 (88)	48 (89)	16 (89)	15 (94)	16 (84)	20 (87)	5 (100)	13 (87)
[95% CI]	[74–96]	[77–96]	[65–99]	[70–100]	[60–97]	[66–97]	[48–100]	[60–98]
Median TTR, months	1.4	1.4	1.4	1.5	1.5	1.4	1.4	1.5
[Range]	[1.2–7.0]	[1.2–9.6]	[1.2–6.9]	[1.2–9.6]	[1.2–7.0]	[1.2–7.0]	[1.3–2.8]	[1.2–8.3]
Median DoR, months	NE	12.9	NE	12.9	12.0	14.6	NE	18.1
[95% CI]	[9.7–NE]	[5.7–NE]	NE	[4.1–NE]	[4.2–NE]	[4.2–NE]	[5.5–NE]	[4.1–NE]

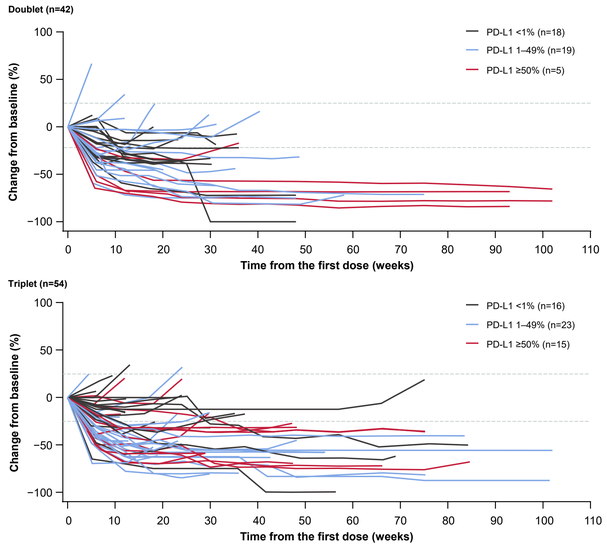
[a]Evaluated locally by tumor proportion score using immunohistochemistry (22C3 assay). [b]Responses with confirmed CR/PR.

Best overall tumor change from baseline in 1L patients



Patients with no baseline target lesions or no postbaseline tumor assessments were excluded from the waterfall plot.

Percent change from baseline in sum of diameter over time in 1L patients by PD-L1 status



Safety summary of 1L patients

Event, n (%)	Doublet (n=42)	Triplet (n=54)
Any TEAE[a]	40 (95)	54 (100)
Study treatment-related[b]	39 (93)	54 (100)
Any grade ≥3 TEAE	24 (57)	41 (76)
Study treatment-related[b]	14 (33)	30 (56)
Any serious TEAEs	16 (38)	24 (44)
Study treatment-related[b]	5 (12)	12 (22)
TEAEs associated with:		
Dose reduction of any drug	9 (21)	10 (19)
Dose reduction of Dato-DXd	9 (21)	7 (13)
Discontinuation of any drug	12 (29)	24 (44)
Discontinuation of Dato-DXd	12 (29)	21 (39)
Death	1 (2)	5 (9)

[a]TEAEs were defined as AEs with a start or worsening date on or after the start of study treatment until 37 days after the end date of study treatment. [b]Drug-related TEAEs may be associated with any component of the study treatment: Dato-DXd, pembrolizumab, cisplatin, or carboplatin.

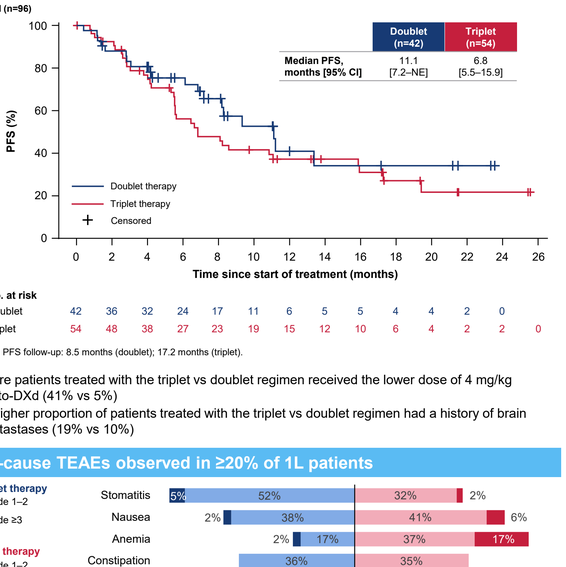
- TEAEs associated with discontinuation of Dato-DXd occurred in 29% of 1L patients receiving the doublet regimen and in 39% of 1L patients receiving the triplet regimen
- The most frequent TEAEs of any grade were stomatitis, nausea, anemia, constipation, and decreased appetite
- Hematologic toxicities such as anemia, platelet count decreased, neutropenia, and neutrophil count decreased occurred more frequently in the triplet cohorts

AESIs in 1L patients

AESI, n (%)	Doublet (n=42)		Triplet (n=54)	
	All grades	Grade 3	All grades	Grade 3
Oral mucositis/stomatitis	26 (62)	2 (5)	22 (41)	1 (2)
Adjudicated drug-related ILD/pneumonitis	10 (24)	2 (5)	14 (26)	1 (2)
Ocular surface events	9 (21)	1 (2)	16 (30)	2 (4)

- Oral mucositis/stomatitis was the most common AESI and was predominantly grade 1/2
- There were no grade 4 or 5 events for any AESI, including adjudicated drug-related ILD/pneumonitis

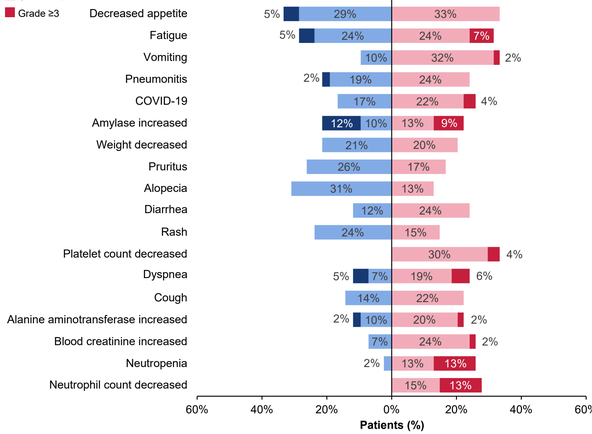
PFS in 1L patients



Median PFS follow-up: 8.5 months (doublet); 17.2 months (triplet).

- More patients treated with the triplet vs doublet regimen received the lower dose of 4 mg/kg Dato-DXd (41% vs 5%)
- A higher proportion of patients treated with the triplet vs doublet regimen had a history of brain metastases (19% vs 10%)

All-cause TEAEs observed in ≥20% of 1L patients



Abbreviations

1L, first-line; ADC, antibody–drug conjugate; AE, adverse event; AESI, adverse event of special interest; AUC, area under the curve; BOR, best overall response; CI, confidence interval; COVID-19, coronavirus disease 2019; CR, complete response; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DoR, duration of response; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IgG1, immunoglobulin G1; ILD, interstitial lung disease; IO, immuno-oncology; IV, intravenous; mAb, monoclonal antibody; NE, non-evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; pembro, pembrolizumab; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; Q3W, every 3 weeks; SD, stable disease; TEAE, treatment-emergent adverse event; TROP2, trophoblast cell surface antigen 2; TTR, time to recurrence.

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