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Daiichi-Sankyo

ASCO Highlights 2024

DAIICHI SANKYO CO., LTD.

June 3rd (US)/ 4th (JP), 2024

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ASCO Highlights 2024: IR conference call

Hiroyuki Okuzawa
President and COO

Ken Takeshita
Head of Global R&D

Mark Rutstein
Head of Global Oncology Development

Content will be delivered on-demand after the meeting

Agenda

1. Welcome message
2. R&D strategy
3. Highlights from ASCO 2024
4. Q&A

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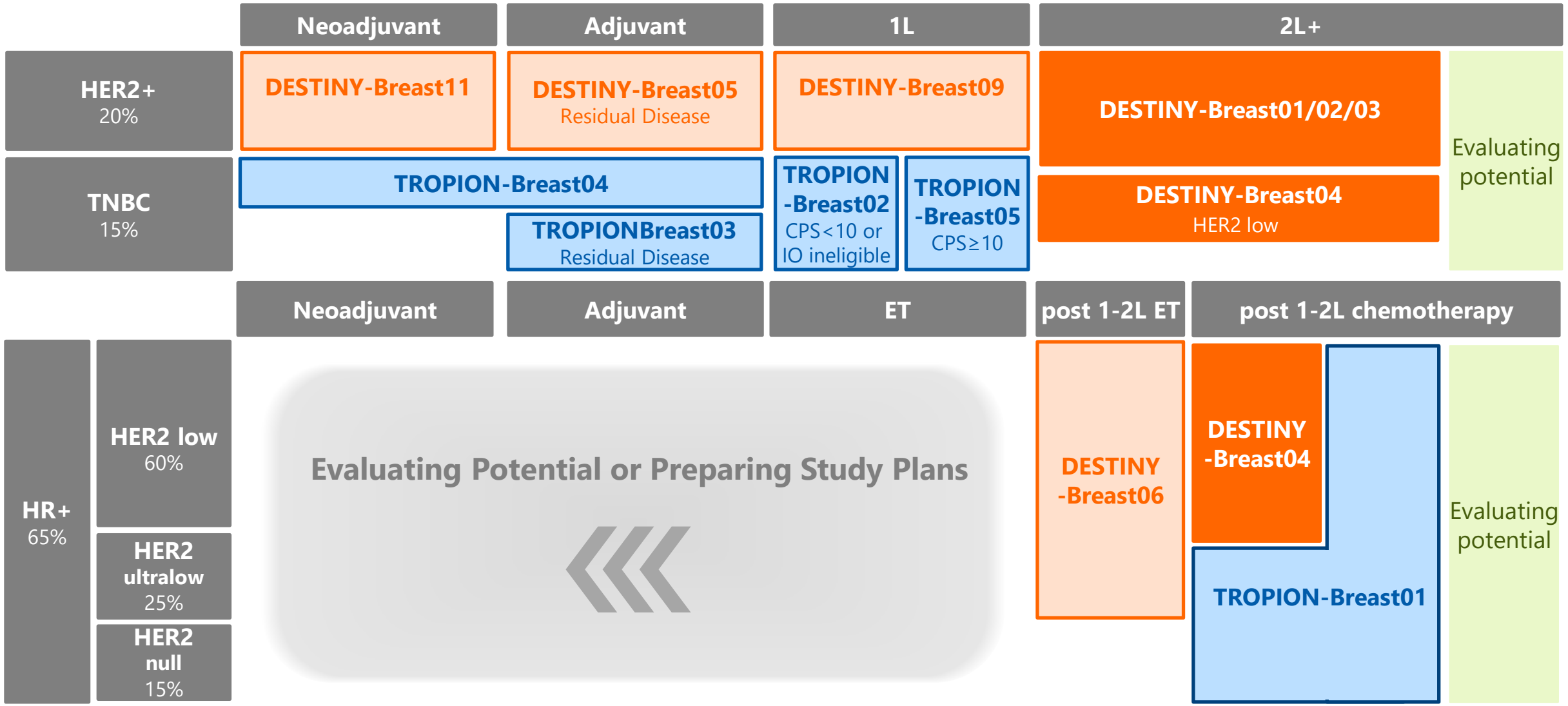
ASCO 2024

With over 30 presentations* across 8 assets and multiple tumor types,
Daiichi Sankyo has delivered scientific outcome not limited to but highlighted by;

- **Substantial progress in ENHERTU breast cancer development**
  - ✓ Highlights IR call discusses DESTINY-Breast06, DESTINY-Breast03 and DESTINY-Breast07
- **Steady progress in lung cancer development among DXd ADCs**
  - ✓ Highlights IR call discusses DESTINY-Lung02 and TROPION-Lung02

* 5 online abstract publications (T-DXd) are included

Establish and expand DXd ADCs to address the broader spectrum of Breast Cancer

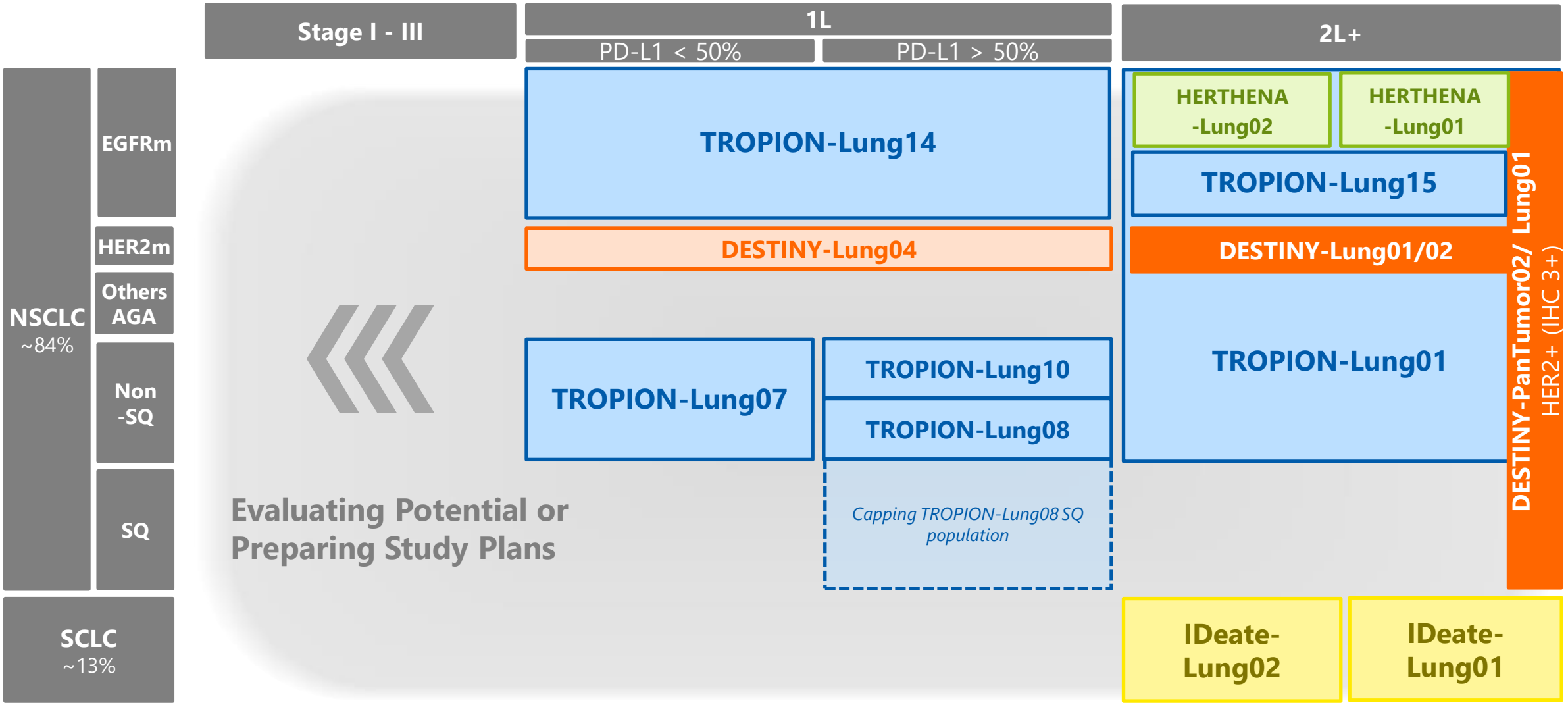


Launched | On-going | ENHERTU® | Dato-DXd | HER3-DXd

- Box size does not reflect the patient population

Pivotal studies only (not exhaustive). CPS, combined positive score; ET, endocrine therapy; HR, hormone receptor; IHC: immunohistochemistry, pCR: pathological complete response, TNBC, triple-negative breast cancer

Establish and expand DXd ADCs to address the broader spectrum of Lung Cancer



Launched | On-going | ENHERTU® | Dato-DXd | HER3-DXd | I-DXd

- Pivotal studies and major Ph2 only, not exhaustive
- Box size does not reflect the patient population

ADC: antibody-drug conjugate, AGA: actionable genomic alteration, Non-SQ: non- squamous, NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer, SQ: squamous

Dato-DXd

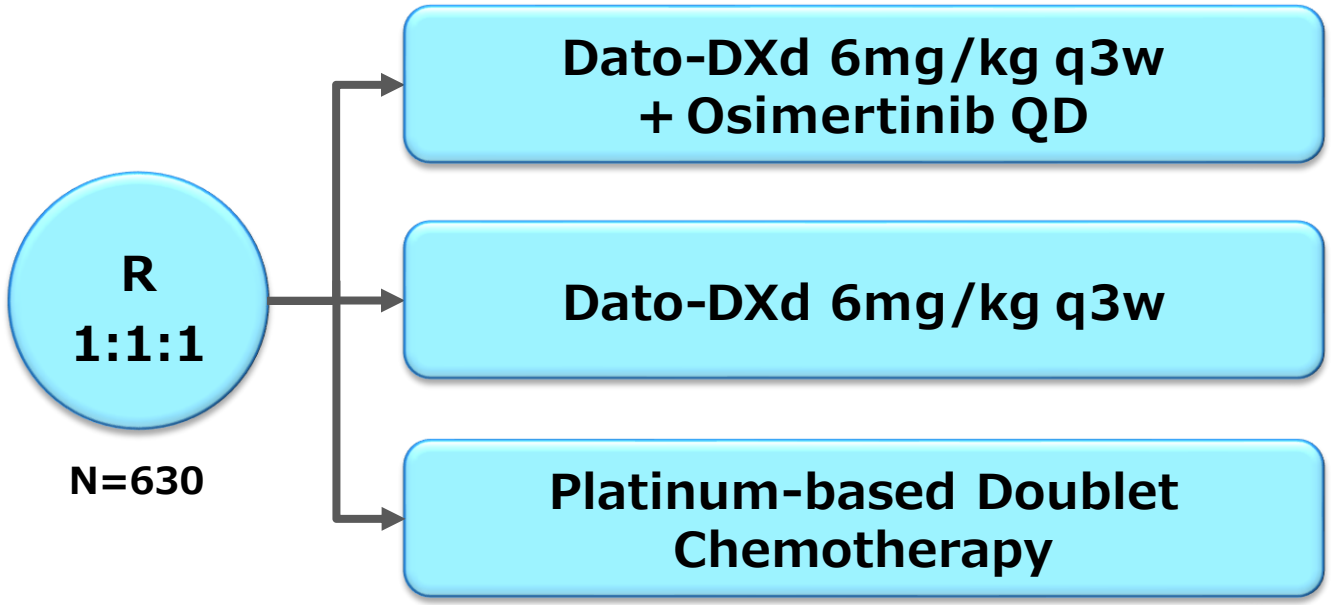
TROPION-Lung15 study

New Ph3 study in 2L EGFR mutated NSCLC for Dato-DXd monotherapy and Osimertinib combination comparing to PBC

TROPION-Lung15 study design

Key Eligibility

- Advanced or metastatic NSCLC who have progressed on prior Osimertinib
- ≤ 2 prior lines of EGFR TKI treatments
- Sensitizing EGFR mutations



- Two primary endpoints for Dato-DXd monotherapy and combination were set independently
- Study start planned in FY2024 H1

Primary endpoint
- PFS (assessed by BICR) mono vs CTX
- PFS (assessed by BICR) combo vs CTX

Secondary endpoint
- OS, PFS (inv assessed), ORR, DOR, DCR, Safety

BICR: blinded independent central review, CTX: 5-Fluorouracil, folinic acid and cisplatin, DCR: disease control rate, DOR: duration of response, NSCLC: non small cell lung cancer, ORR: objective response rate, OS: overall survival, PBC: platinum-based chemotherapy, PFS: progression-free survival, QD: quaque die, q3w: every 3 weeks, TKI: tyrosine kinase inhibitor

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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

Giuseppe Curigliano
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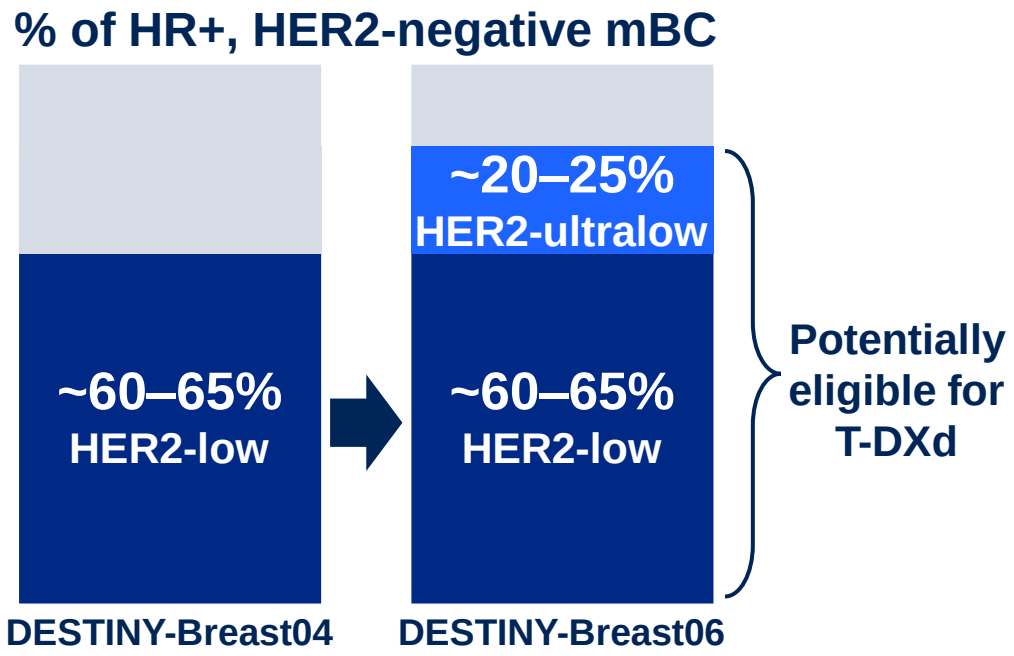
Additional authors: Xichun Hu, Rebecca Dent, Kan Yonemori, Carlos H Barrios, Joyce A O'Shaughnessy, Hans Wildiers, Qingyuan Zhang, Seock-Ah Im, Cristina Saura, Laura Biganzoli, Joohyuk Sohn, Christelle Lévy, William Jacot, Natasha Begbie, Jun Ke, Gargi Patel, Aditya Bardia

On behalf of the DESTINY-Breast06 investigators

DESTINY-Breast06: key takeaways



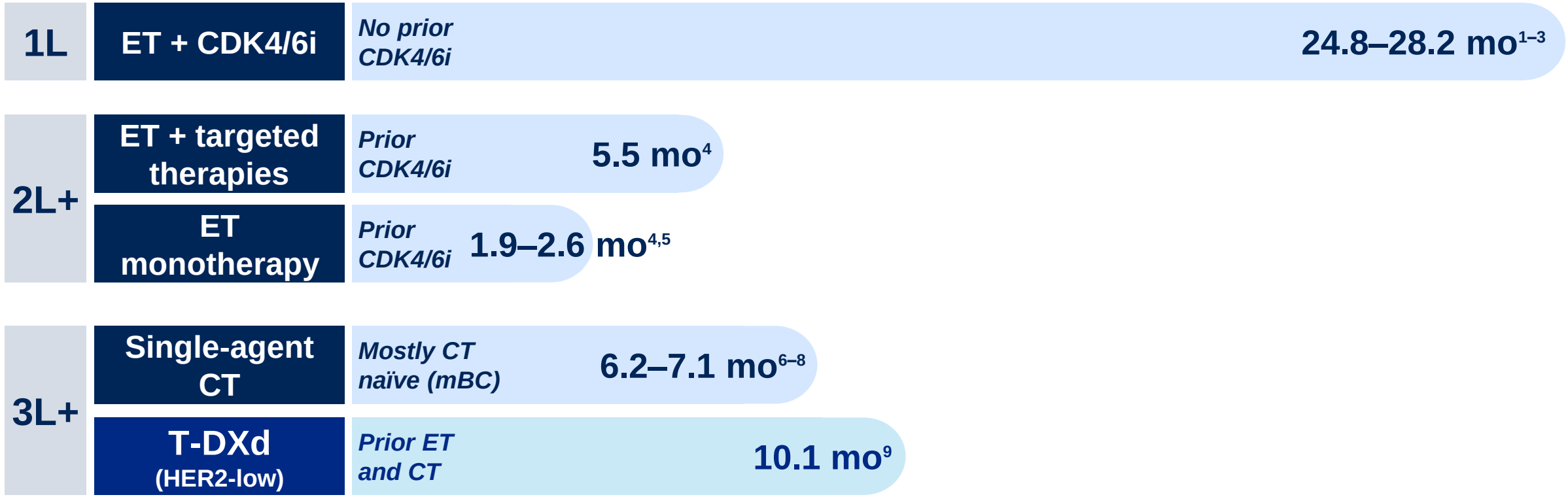
- T-DXd demonstrated efficacy in **HER2-low mBC** in an **earlier line of treatment** to DESTINY-Breast04
- Including HER2-ultralow, the proportion of patients who could benefit from T-DXd is **~85% of HR+, HER2-negative mBC** after DESTINY-Breast06

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

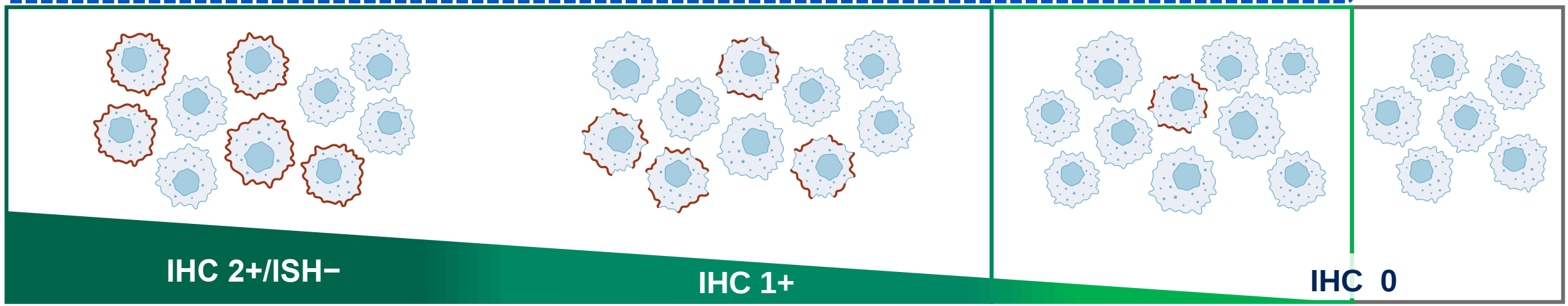
Targeting ‘low’ and ‘ultralow’ HER2-expressing tumors in mBC

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

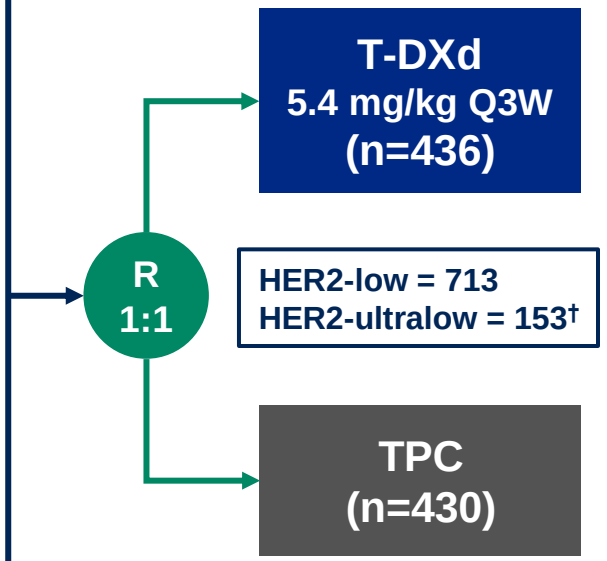
- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

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)



ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

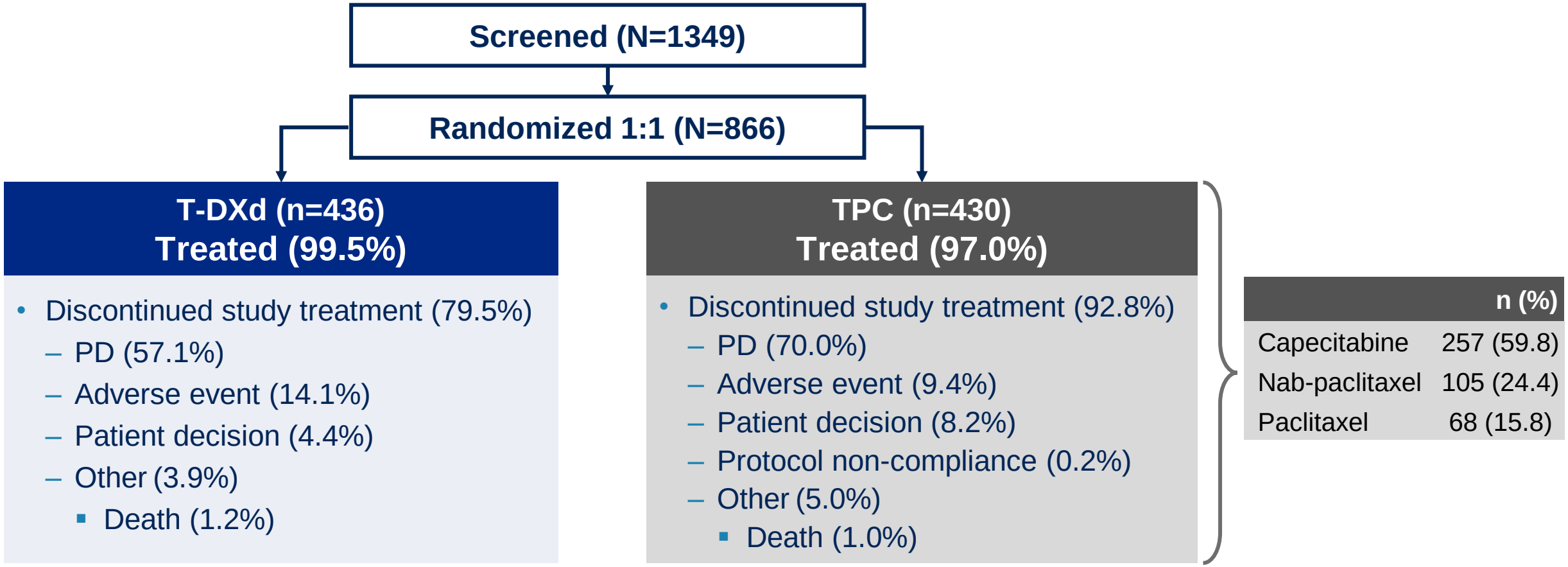
- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

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)

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

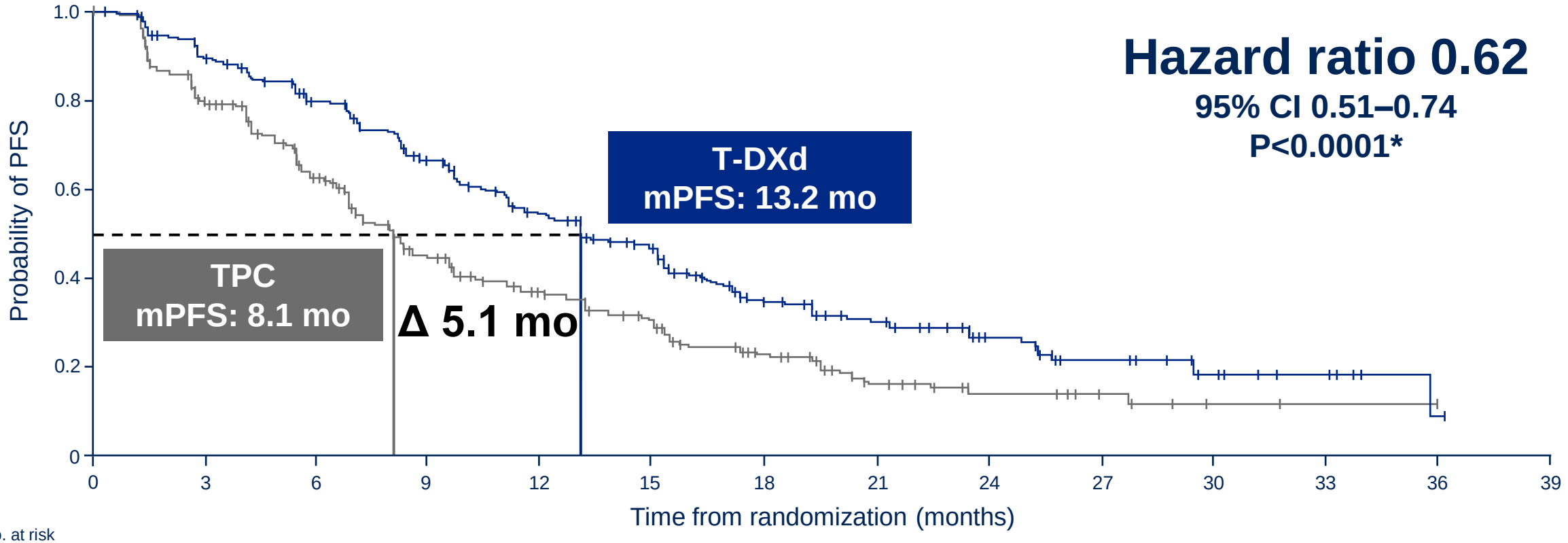
Prior therapies

	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*

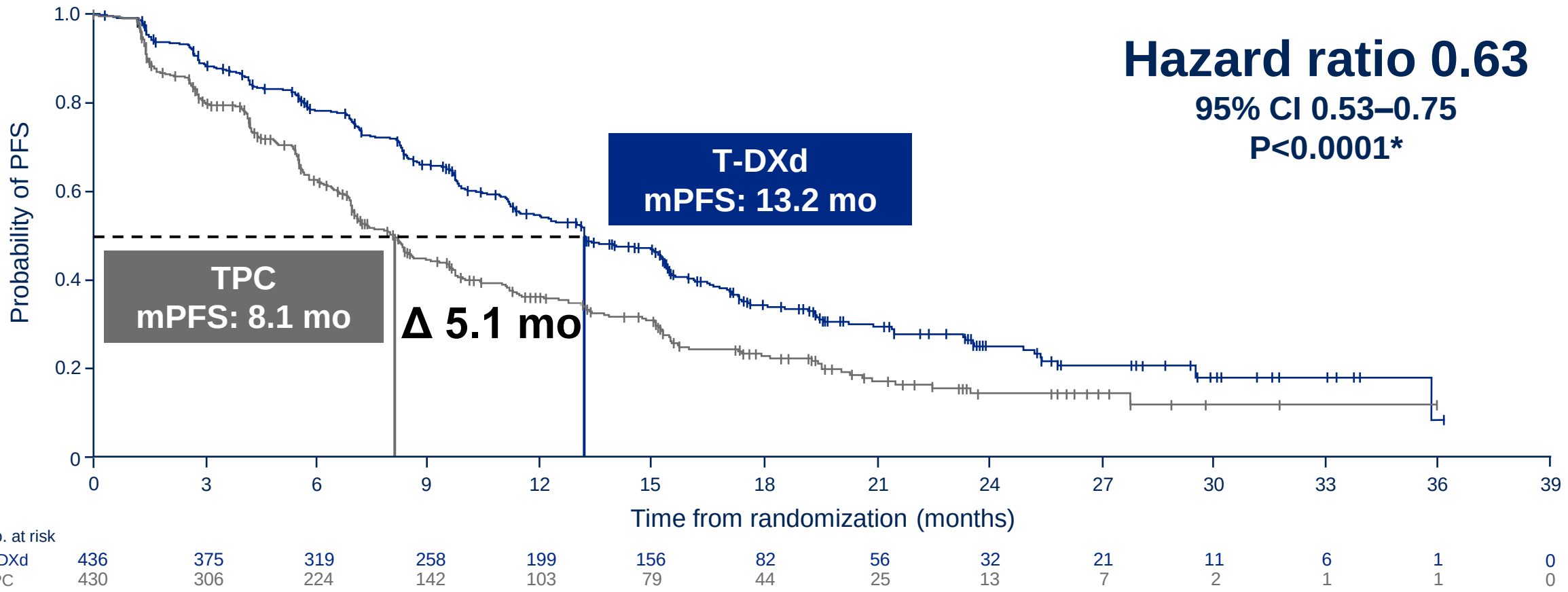
No. at risk

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



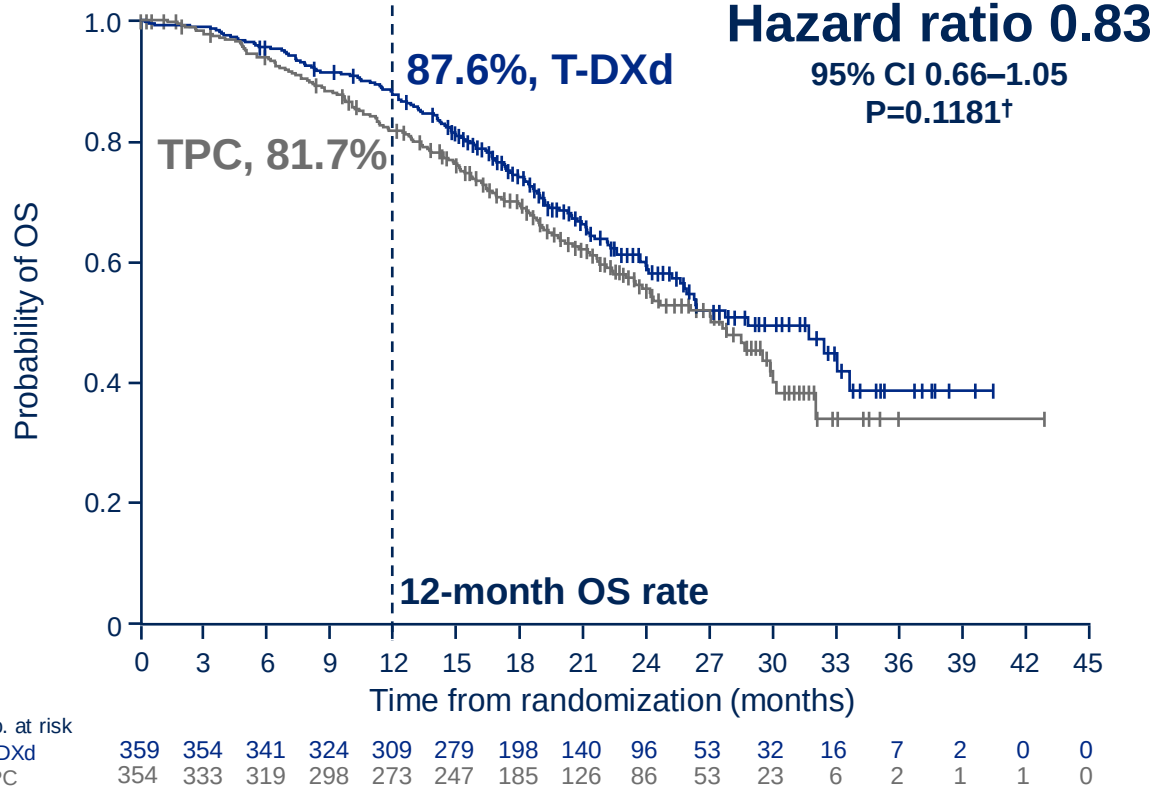
T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in ITT

*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



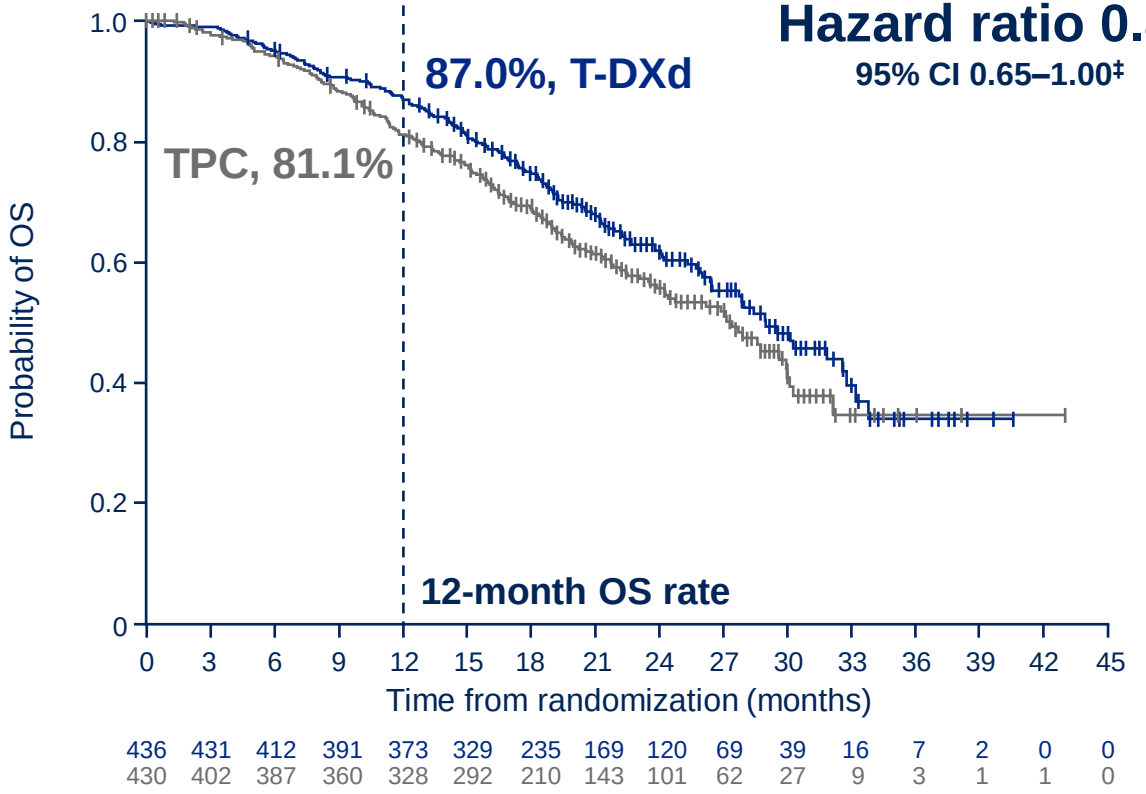
No. at risk

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)

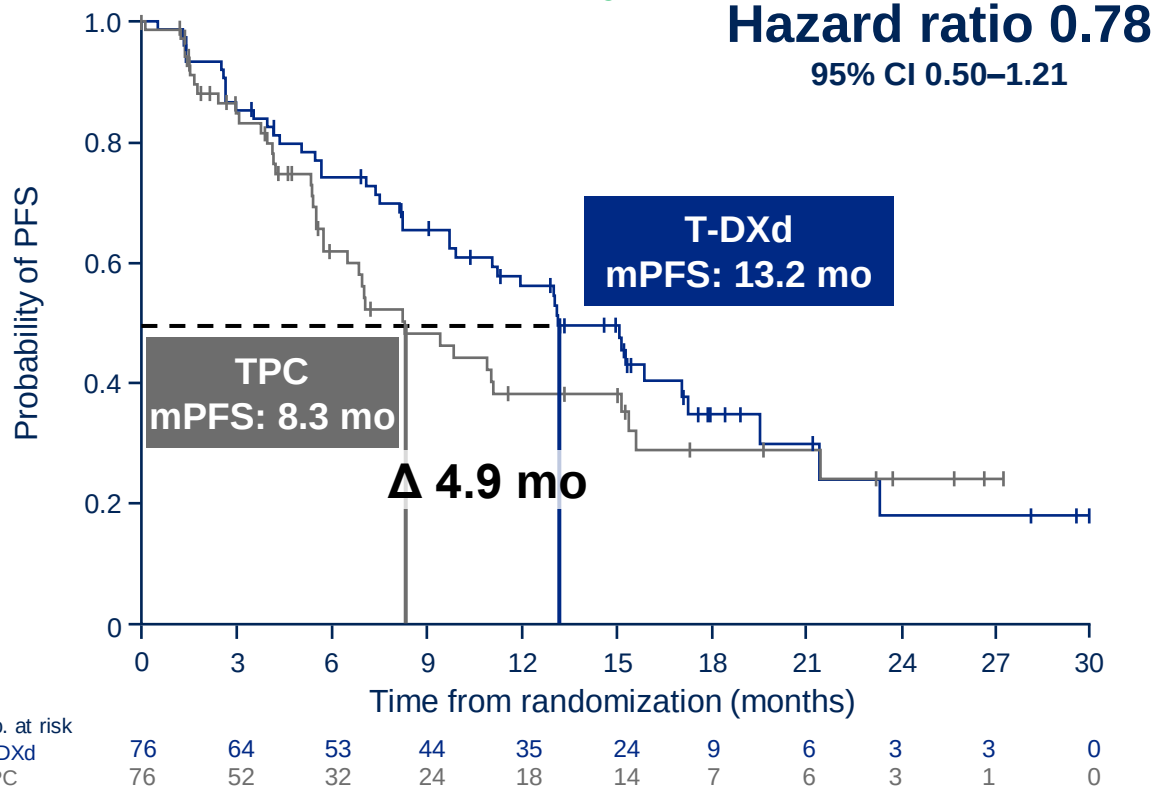
*39.6% maturity (of total N for population) at this first interim analysis; median duration of follow up was 18.6 months (HER2-low); †P-value of <0.0046 required for statistical significance; ‡no test of significance was performed in line with the multiple testing procedure; median duration of follow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

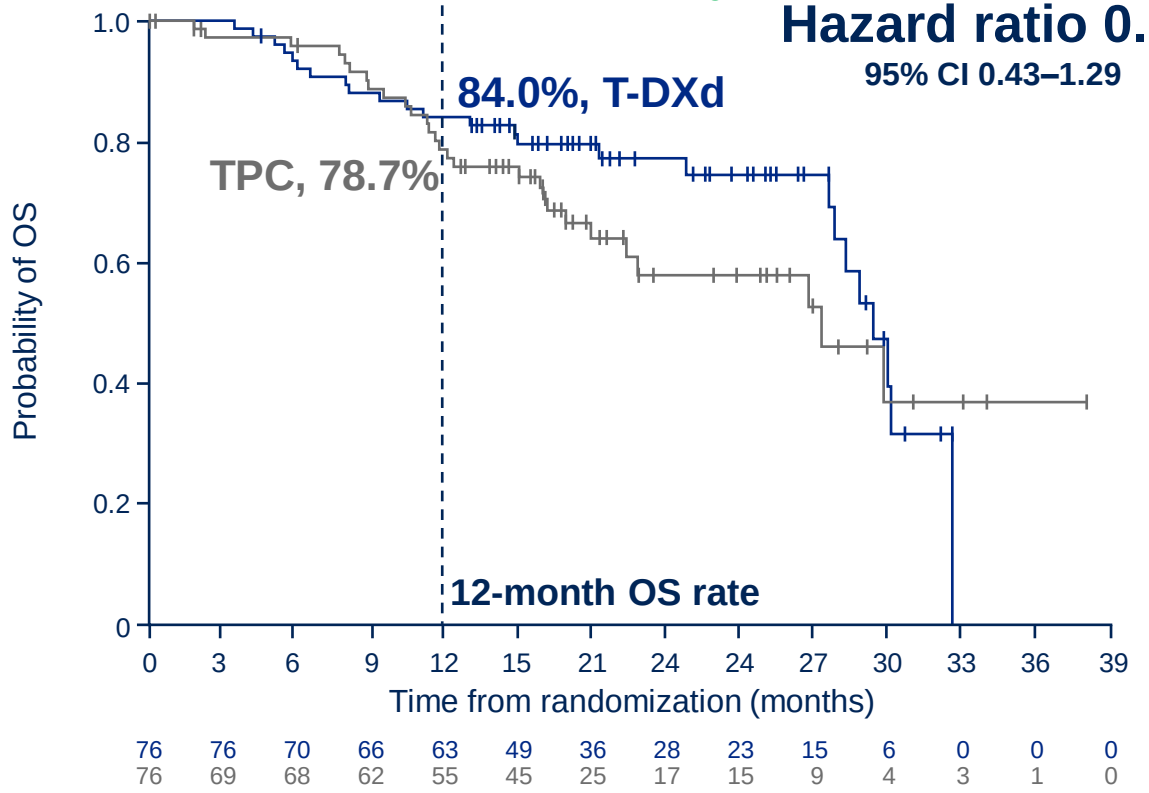
PFS (BICR)

n=152



OS*

n=152



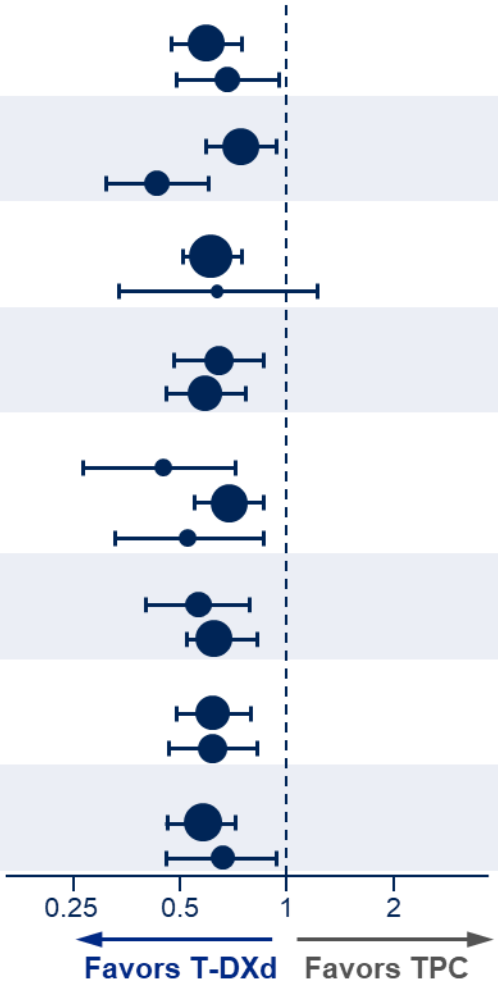
PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*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)

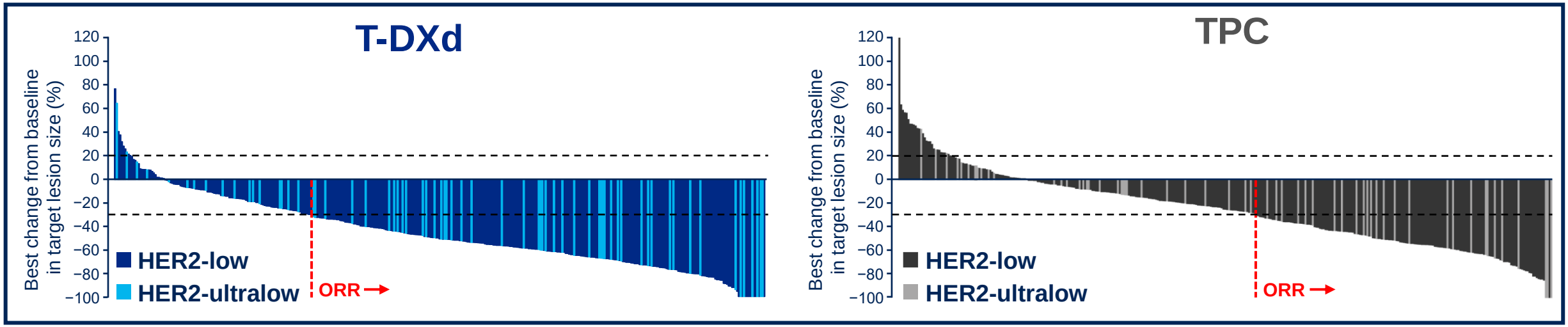


Size of circle is proportional to the number of events

*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

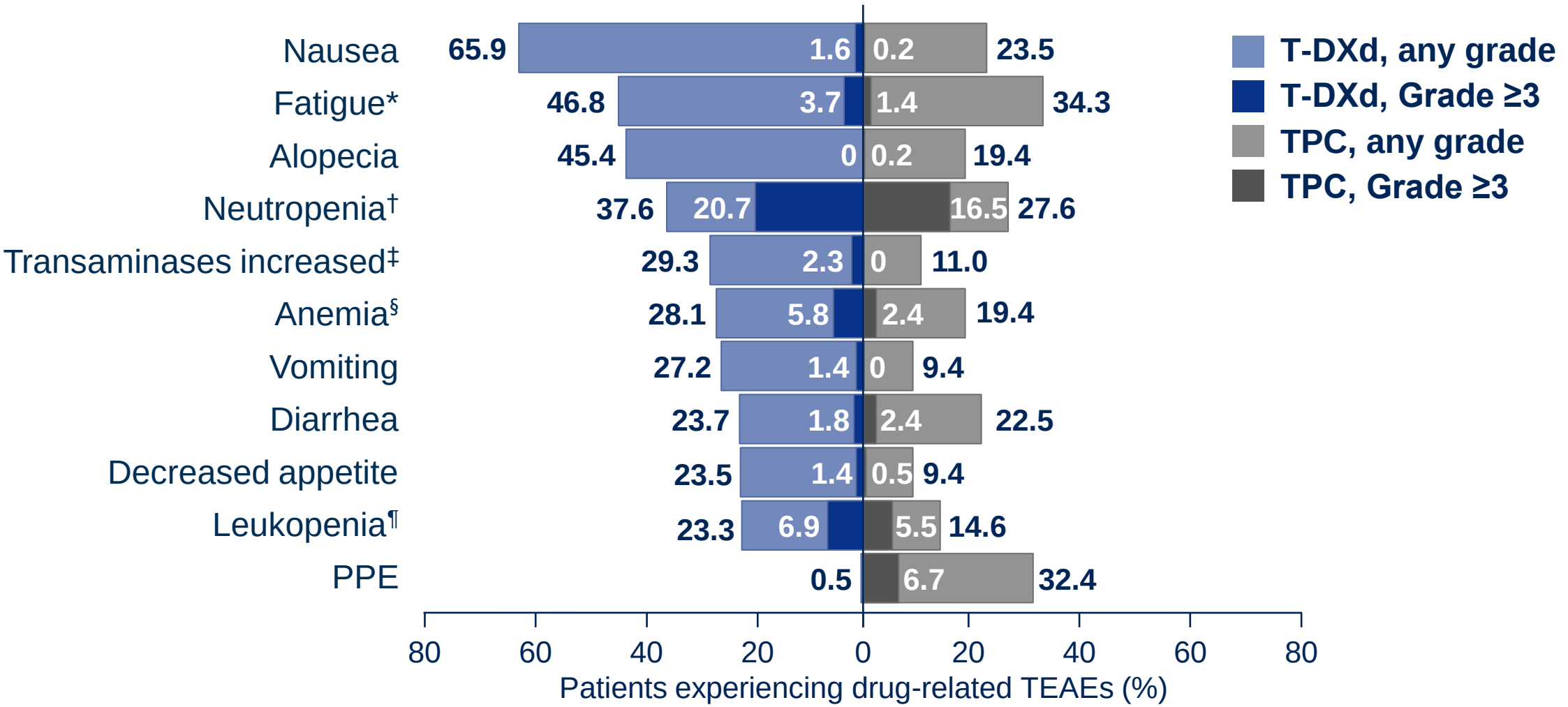
Overall safety summary

	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†

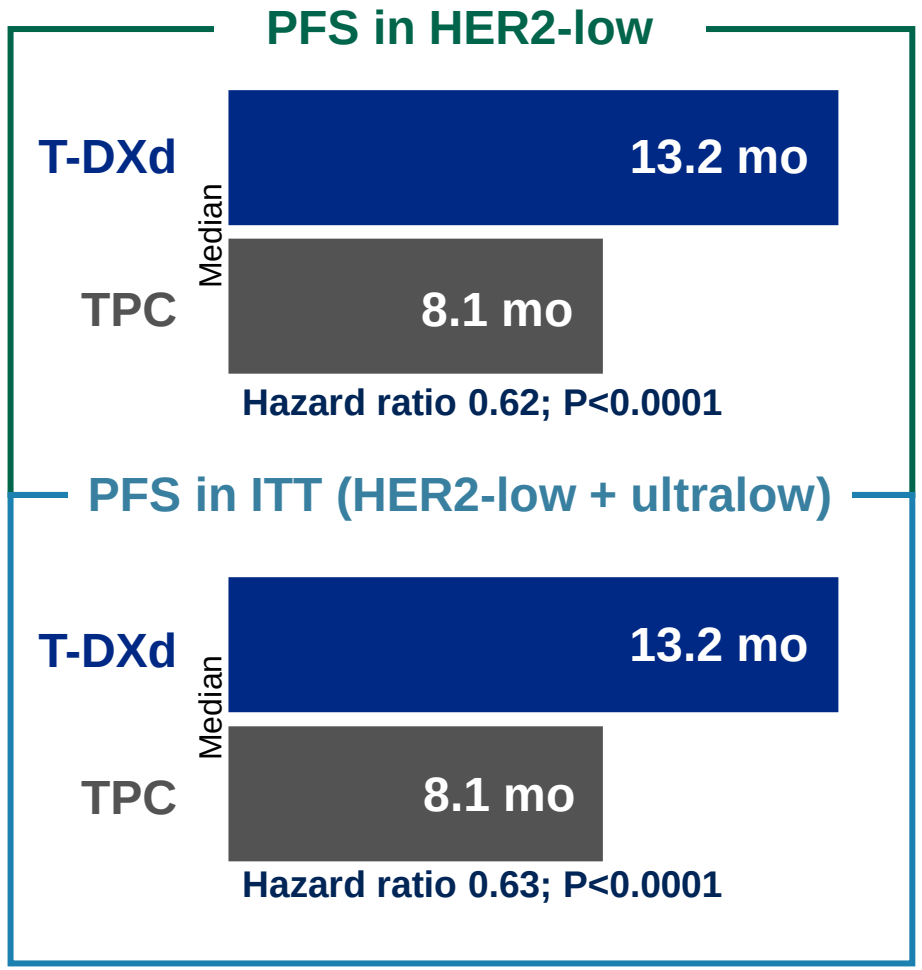
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Ejection fraction decreased						
T-DXd (n=434)	1 (0.2)	31 (7.1)	3 (0.7)	0	0	35 (8.1)
TPC (n=417)	0	11 (2.6)	1 (0.2)	0	0	12 (2.9)
Cardiac failure						
T-DXd (n=434)	0	0	0	0	0	0
TPC (n=417)	0	1 (0.2)	1 (0.2)	1 (0.2)	0	3 (0.7)

*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

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

Poster #1025

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

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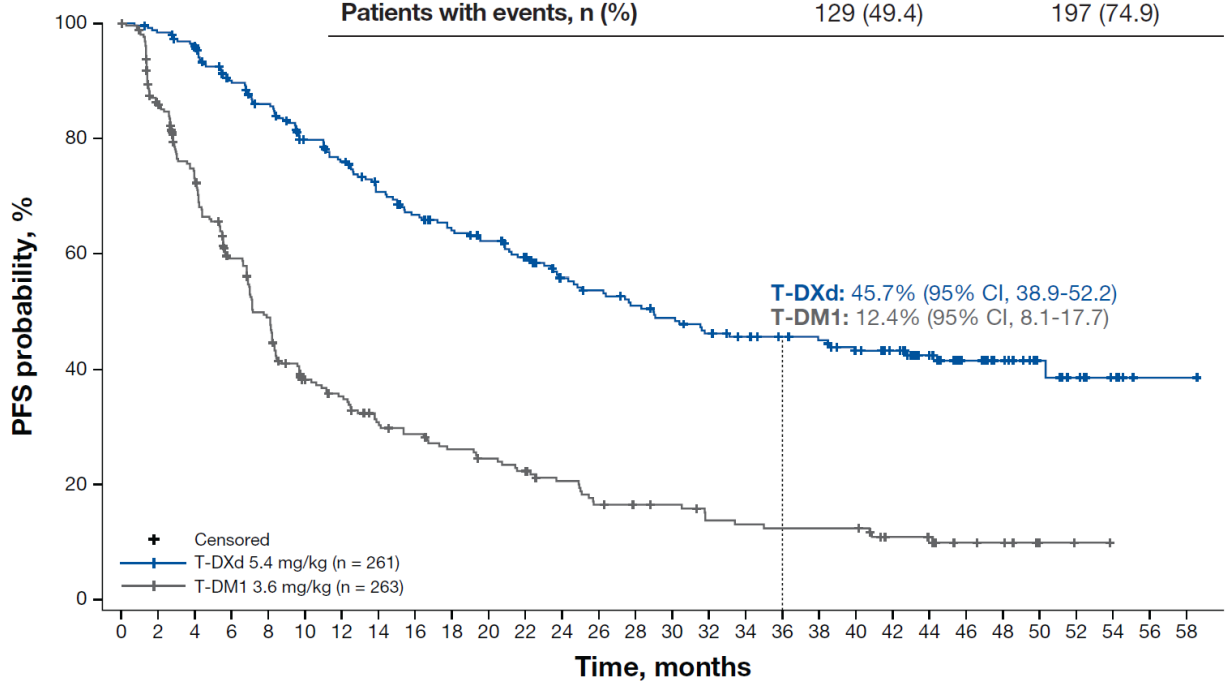
Figure 3. PFS by Investigator Assessment

	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)

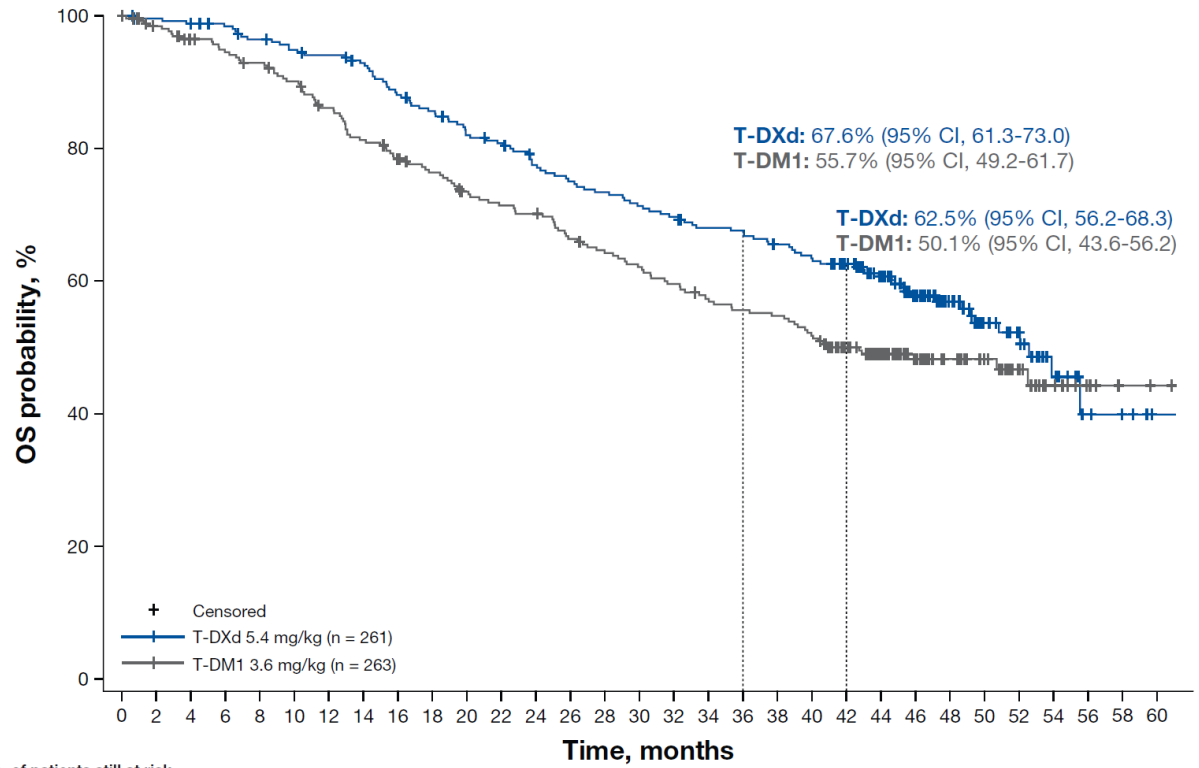


No. of patients still at risk

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
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		

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

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.

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)

[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.

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

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)

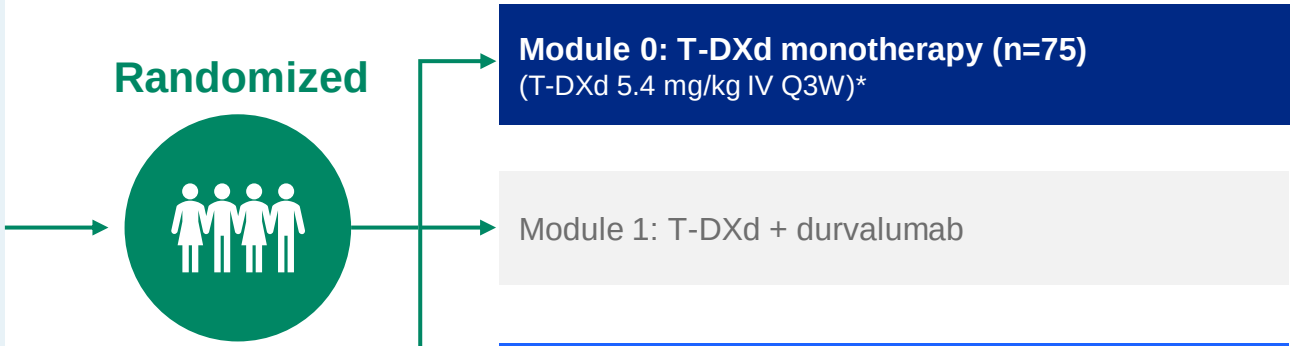
PATIENT POPULATION

- 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

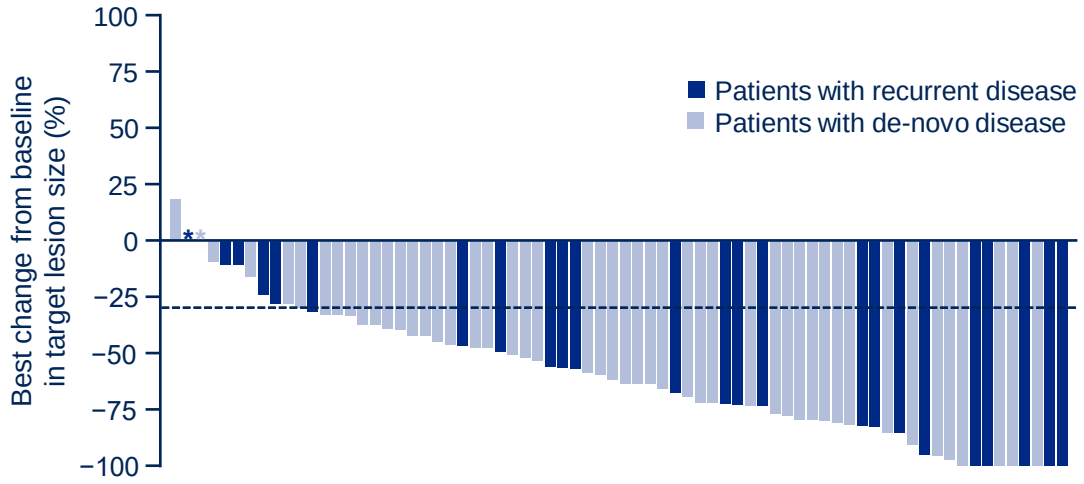
Patient disposition

	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

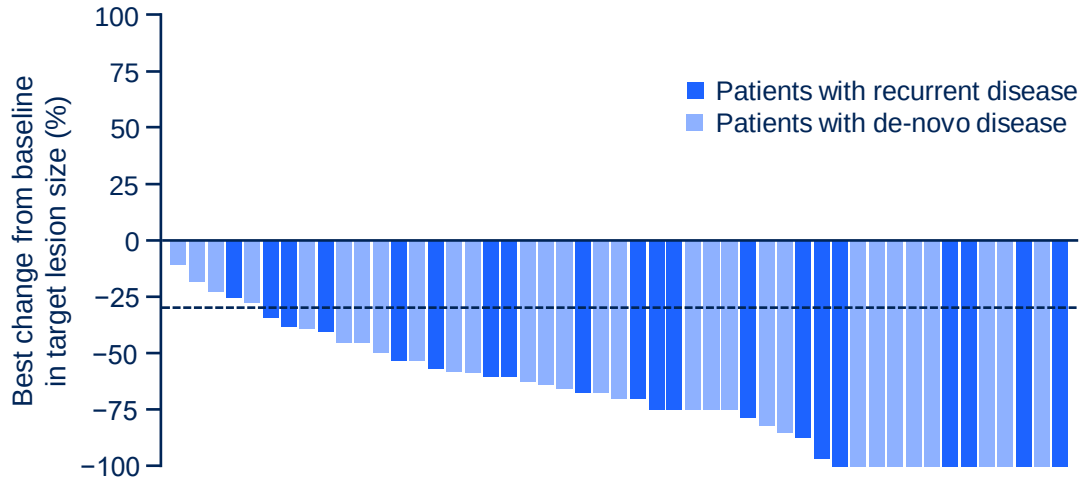
Response to treatment per RECIST 1.1 by investigator

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)

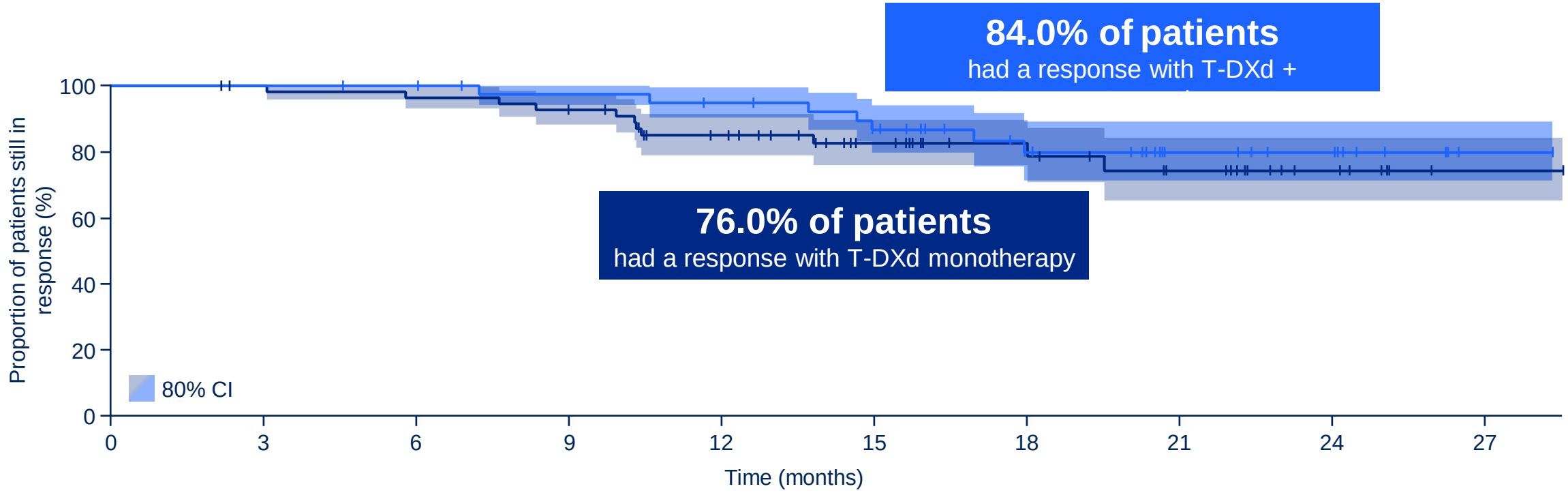
T-DXd + pertuzumab (n=50)



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

Duration of response



Number at risk

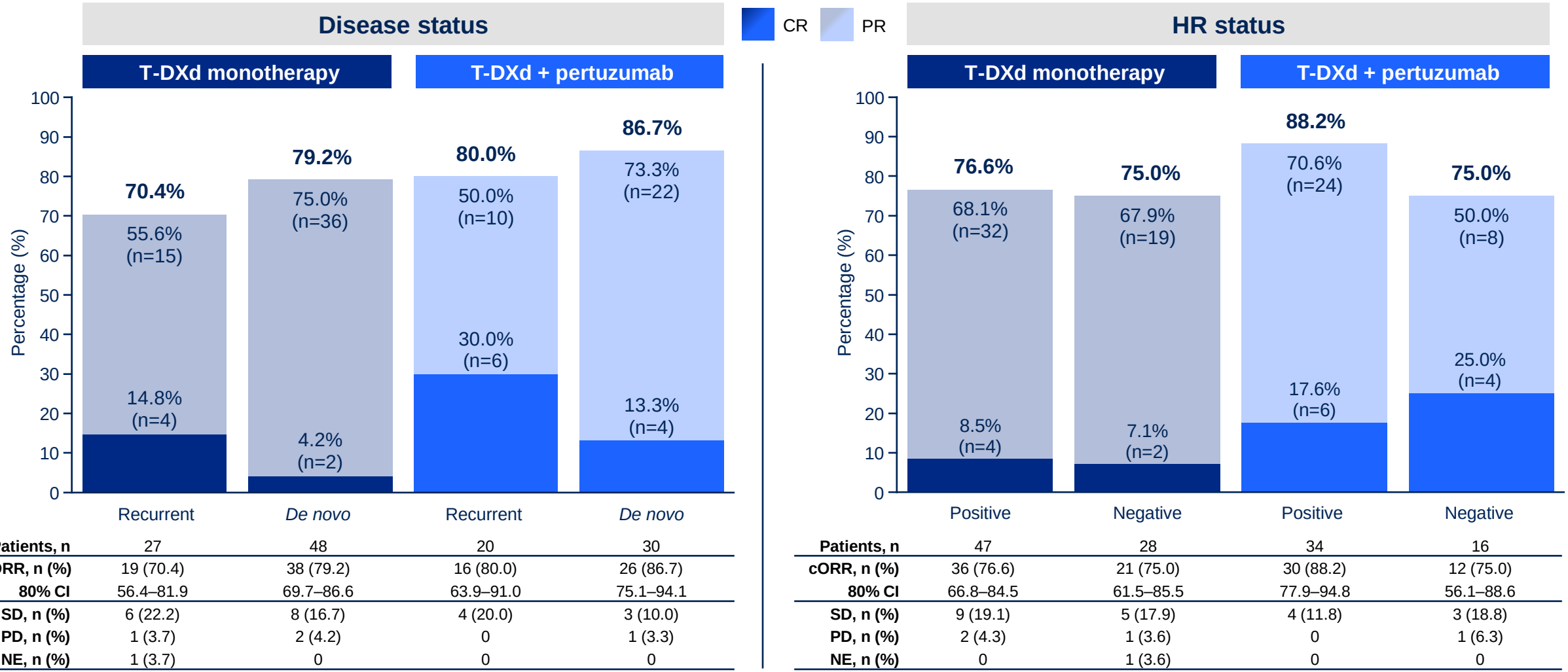
T-DXd monotherapy	57	55	53	50	41	28	21	15	7	1
T-DXd + pertuzumab	42	42	41	38	36	31	21	13	10	1

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

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

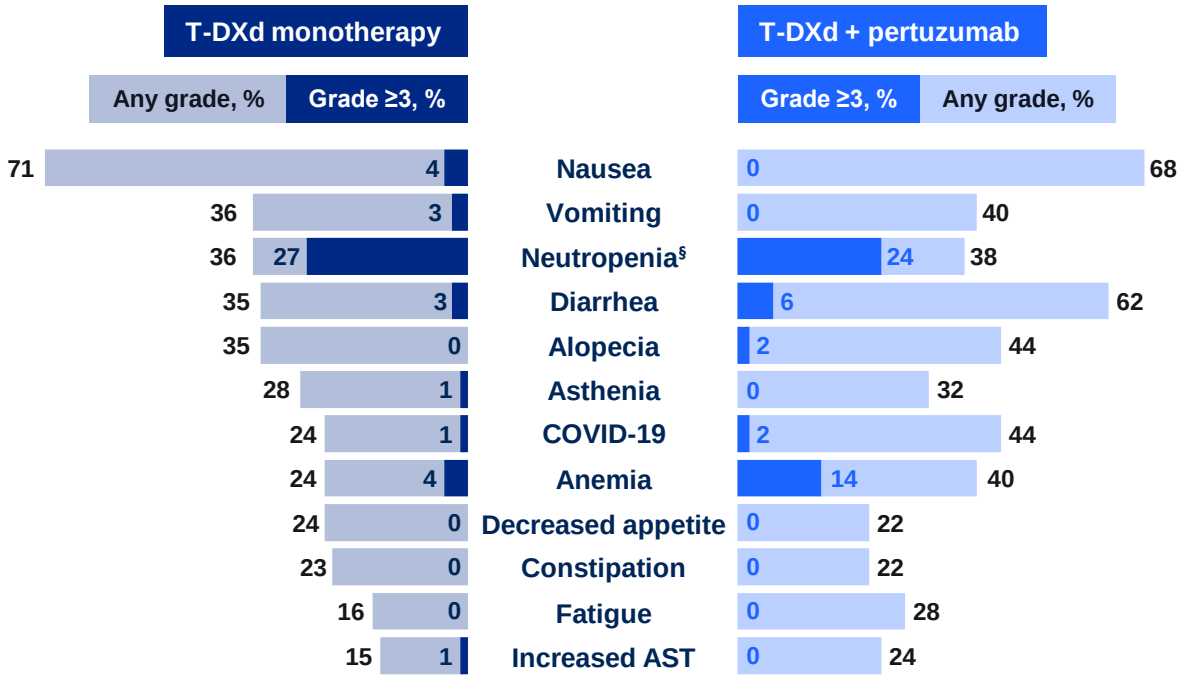
DCO was December 22, 2023

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

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

- 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
- 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

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
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

Poster #8543

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

Pasi A. Jänne,[1] Yasushi Goto,[2] Toshio Kubo,[3] Kiichiro Ninomiya,[3] Sang-We Kim,[4] David Planchard,[5] Myung-Ju Ahn,[6] Egbert Smit,[7] Adrianus Johannes de Langen,[7] Maurice Pérol,[8] Elvire Pons-Tostivint,[9] Silvia Novello,[10] Hidetoshi Hayashi,[11] Junichi Shimizu,[12] Dong-Wan Kim,[13] Kaline Pereira,[14] Fu-Chih Cheng,[14] Ayumi Taguchi,[15] Yingkai Cheng,[14] Kyle Dunton,[16] Ahmed Ali,[17] Koichi Goto[18]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]National Cancer Center Hospital, Tokyo, Japan; [3]Okayama University Hospital, Okayama, Japan; [4]Asan Medical Center, Seoul, Republic of Korea; [5]Gustave Roussy, Thoracic Group, Villejuif, and Paris-Saclay University, Paris, France; [6]Samsung Medical Center, Seoul, Republic of Korea; [7]Netherlands Cancer Institute, Amsterdam, Netherlands; [8]Centre Léon Bérard, Lyon, France; [9]Centre Hospitalier Universitaire de Nantes, Nantes Université, Nantes, France; [10]University of Turin, Azienda Ospedaliero-Universitaria San Luigi Gonzaga, Turin, Italy; [11]Kindai University Hospital, Osaka, Japan; [12]Aichi Cancer Center Hospital, Nagoya, Japan; [13]Seoul National University Hospital, Seoul, Republic of Korea; [14]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [15]Daiichi Sankyo, Tokyo, Japan; [16]Daiichi Sankyo UK Ltd., Uxbridge, United Kingdom; [17]Daiichi Sankyo Europe GmbH, Munich, Germany; [18]National Cancer Center Hospital East, Kashiwa, Japan

Figure 1. DESTINY-Lung02 Study Design

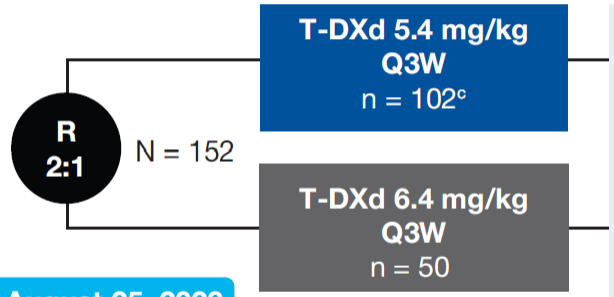
Key Eligibility Criteria[a]
- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:
- Prior anti–PD-(L)1 treatment

Patients and investigators were blinded to the dose level

Final analysis data cutoff: August 25, 2023

Study Design



Primary Endpoint
- Confirmed ORR by BICR

Secondary Endpoints
- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Exploratory Endpoints
- PROs:
  - EQ-5D-5L
  - EORTC QLQ-C30
  - EORTC QLQ-LC13
  - NSCLC-SAQ

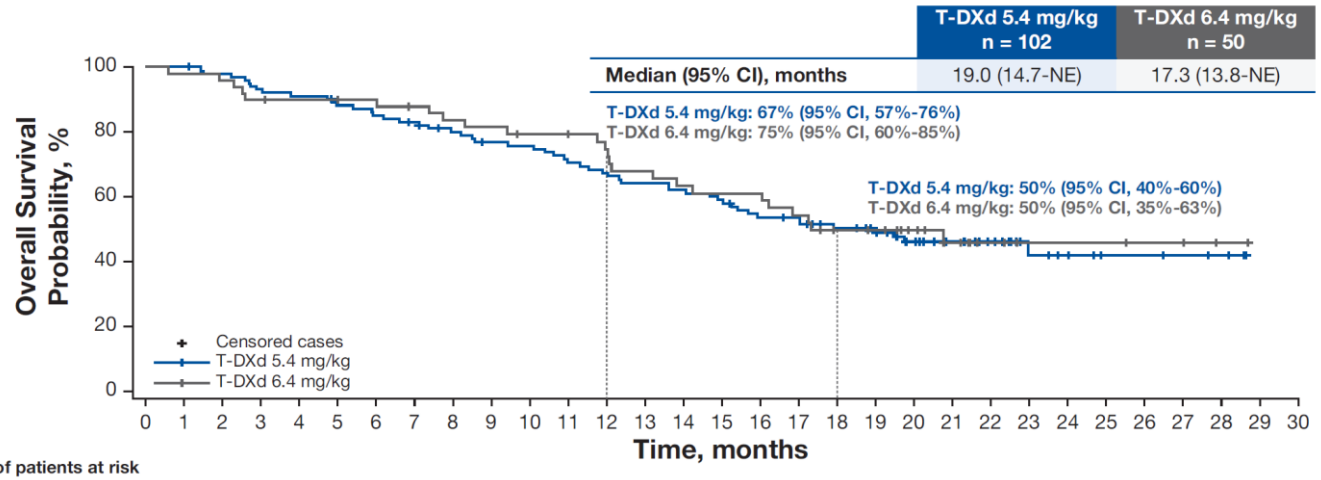
[a]Patients with stable brain metastases at baseline (asymptomatic; not requiring corticosteroid or anticonvulsant treatment) were eligible.
[b]Activating *HER2* mutation documented from an archival or fresh tumor tissue sample by certified local laboratory assessment.
[c]1 patient randomly assigned 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.

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



No. of patients at risk

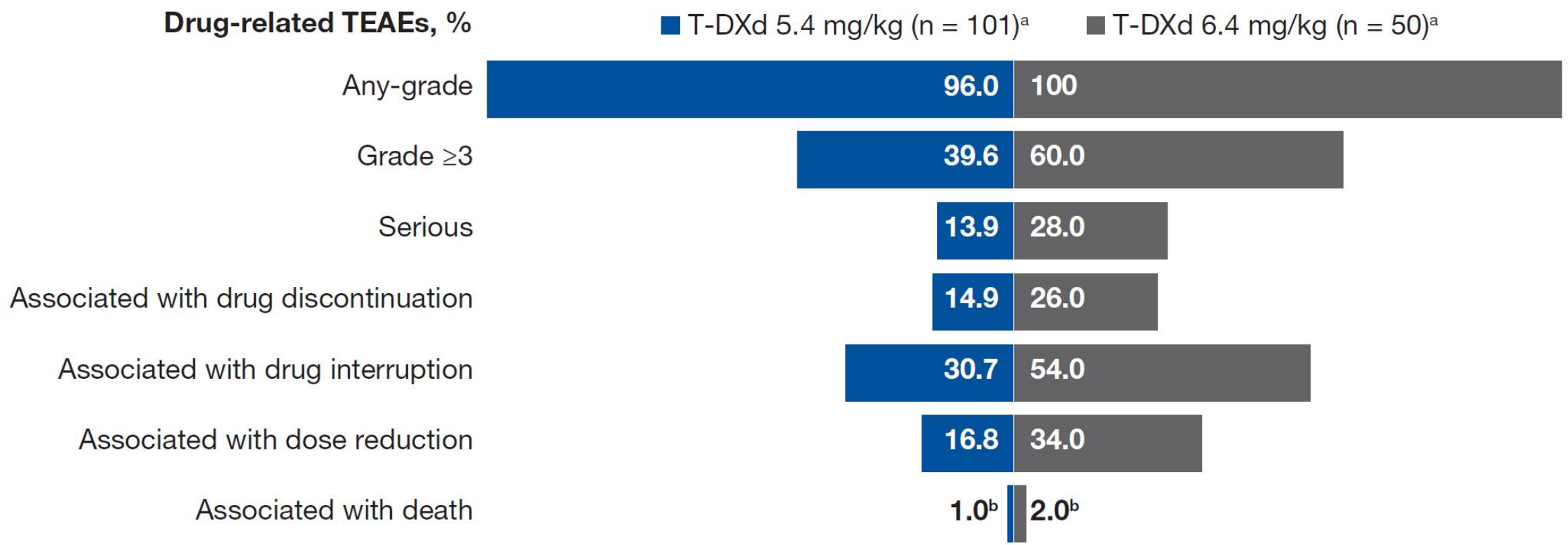
T-DXd 5.4 mg/kg:	102	102	99	94	92	88	85	82	77	73	72	67	64	61	59	56	50	49	43	40	30	23	17	10	8	5	5	4	3	0	0
T-DXd 6.4 mg/kg:	50	49	48	45	44	43	43	41	39	38	36	36	33	30	28	27	27	24	20	19	15	11	6	4	4	4	3	3	1	0	0

No. of events

T-DXd 5.4 mg/kg:	0	0	2	7	9	12	15	17	20	23	24	29	32	35	37	40	45	45	48	48	51	51	51	52	52	52	52	52	52	52	0
T-DXd 6.4 mg/kg:	0	1	2	5	5	5	5	6	8	9	10	10	12	15	17	18	18	21	23	23	23	24	24	24	24	24	24	24	24	24	0

Data cutoff: August 25, 2023.

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.

Poster #8617

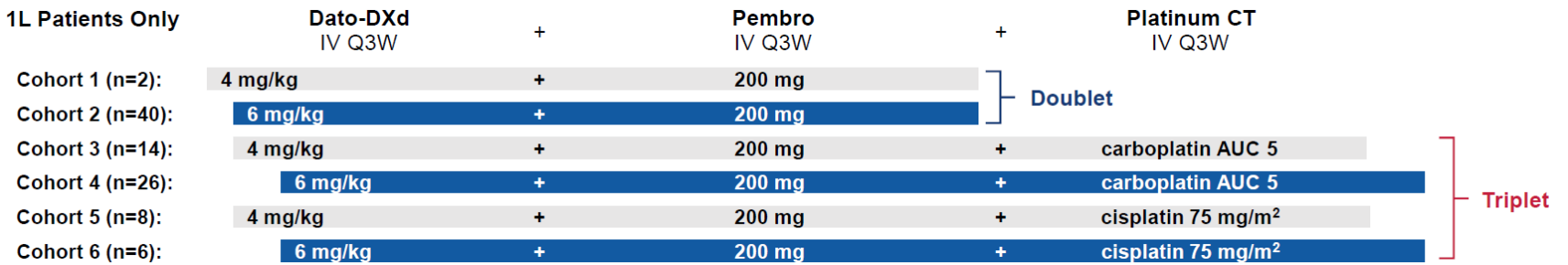
Datopotamab deruxtecan (Dato-DXd) plus pembrolizumab with or without platinum chemotherapy as first-line therapy for advanced non-small cell lung cancer (NSCLC); subgroup analysis from TROPION-Lung02

Benjamin Levy,[1] Luis Paz Ares,[2] Wu Chou Su,[3] Scott Herbert,[4] Tsung Ying Yang,[5] Anthony Tolcher,[6] Yanyan Lou,[7] Yoshitaka Zenke,[8] Diego Cortinovis,[9] Enriqueta Felip,[10] Manuel Domine,[11] Konstantinos Leventakos,[12] Emiliano Calvo,[13] Atsushi Horiike,[14] Edward Pan,[15] Daisy Lin,[15] Xiaoyu Jia,[15] Priyanka Basak,[15] Michael J. Chisamore,[16] Yasushi Goto[17]

[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Medicine, Baltimore, MD, USA; [2]Hospital Universitario 12 de Octubre, CNIO-H12O Lung Cancer Unit, Universidad Complutense & CiberOnc, Madrid, Spain; [3]Department of Oncology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [4]Quantum, Santa Fe, NM, USA; [5]Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [6]NEXT Oncology, San Antonio, TX, USA; [7]Mayo Clinic, Jacksonville, FL, USA; [8]Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [9]Università degli Studi di Milano-Bicocca, Monza, Italy; [10]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [11]Department of Oncology, Hospital Universitario Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain; [12]Mayo Clinic, Rochester, MN, USA; [13]START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [14]Division of Medical Oncology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [15]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [16]Merck & Co., Inc., Rahway, NJ, USA; [17]National Cancer Center Hospital, Tokyo, Japan

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 Jun 30, 2022)[c]
  - Treatment-naïve (cohorts 3-6)[c]



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).

- **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 EG*FR, 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.

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.

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.

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

Agenda

1. Welcome message
2. R&D strategy
3. Highlights from ASCO 2024
4. **Q&A**

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