Post-ASCO update on the evolving management of metastatic HER2-expressing breast cancer

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HARVARD MEDICAL SCHOOL

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Outline

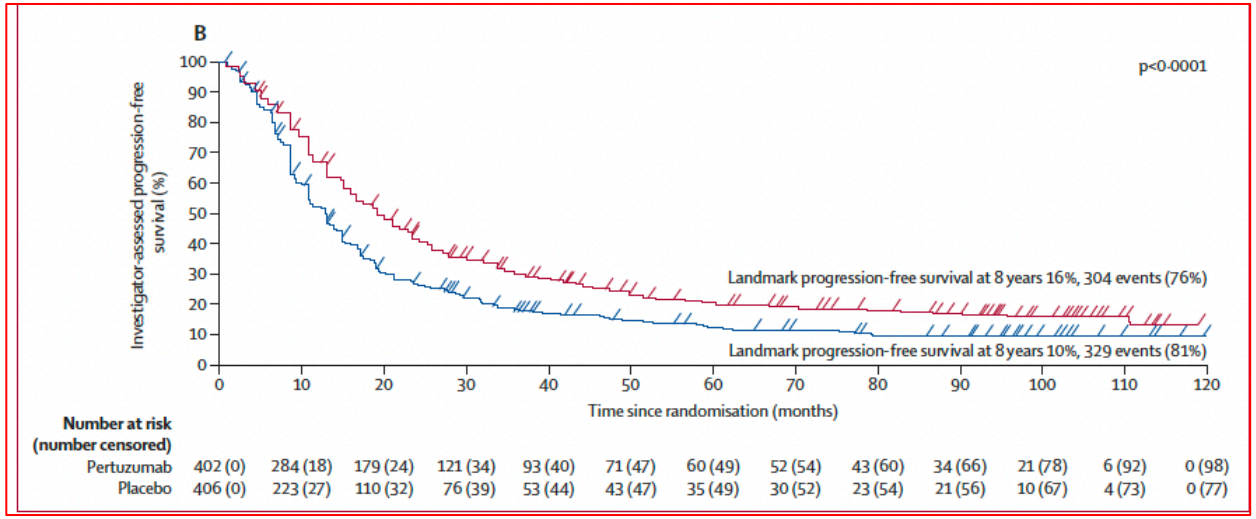
- Selection of first-line therapy for **HER2+ metastatic breast cancer**
- Selection of first-line cytotoxic treatment for endocrine-refractory **HR+ HER2 low/ultralow metastatic breast cancer**
- …*aka: Should T-DXd be first- or second-line?*

Outline

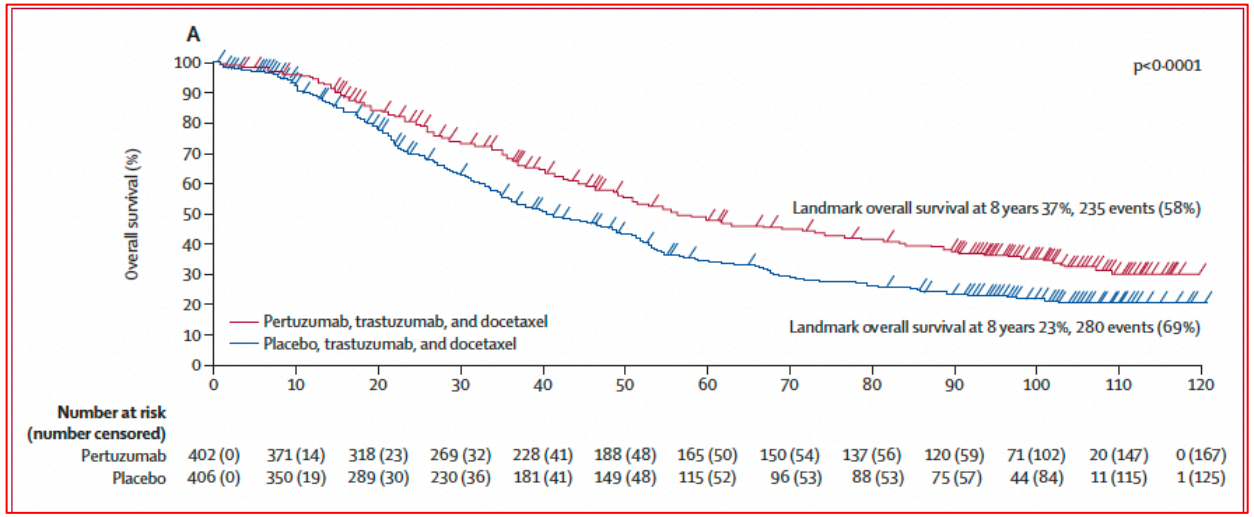
- Selection of first-line therapy for **HER2+ metastatic breast cancer**
- Selection of first-line cytotoxic treatment for endocrine-refractory **HR+ HER2 low/ultralow metastatic breast cancer**

1L HER2+ Metastatic Breast Cancer: CLEOPATRA
End-of-Study Analysis

PFS



OS



mPFS: 18.7 vs 12.4 mos

Landmark PFS at 8 yrs: 16% vs 10%

mOS: 57.1 vs 40.8 mos (Δ16.3 mos)

Landmark OS at 8 yrs : 37% vs 23%

*Concurrent endocrine therapy during H/HP maintenance was not allowed on CLEOPATRA

PRESENTED BY: Claudine Isaacs, MD, FRCPC

Swain S et al. *Lancet Oncol* 2020; 21: 519-30

DESTINY-Breast09 study design

A randomized, multicenter, open-label,* Phase 3 study (NCT04784715)

Eligibility criteria

- HER2+ a/mBC
- Asymptomatic/inactive brain mets allowed
- De-novo vs recurrent mBC
- HR+ or HR−
- *PIK3CA*m (detected vs non-detected)

n=387

T-DXd‡ + placebo

Blinded until final PFS analysis

Endpoints

Primary

- PFS (BICR)

- **Key participant characteristics:**
  - 51% de novo mBC; 54% HR+; ~82% IHC 3+
  - Of those initially diagnosed with early-stage disease: ~ 80-85% received (neo)adjuvant chemo; **~ 58% trastuzumab**; **~15% pertuzumab**; **2% T-DM1**
  - Concurrent use of **ET in HR+**: **13.5% in T-DXd + P arm**; **38.3% in THP arm**

(modified from Isaacs ASCO 2025)

At this planned interim analysis (DCO Feb 26, 2025), results are reported for the T-DXd + P and THP arms

*Open label for THP arm. Double blinded for pertuzumab in experimental arms; †HER2-targeted therapy or chemotherapy; ‡5.4 mg/kg Q3W; §840 mg loading dose, then 420 mg Q3W; ¶paclitaxel 80 mg/m^2 QW or 175 mg/m^2 Q3W, or docetaxel 75 mg/m^2 Q3W for a minimum of six cycles or until intolerable toxicity; ‖8 mg/kg loading dose, then 6 mg/kg Q3W

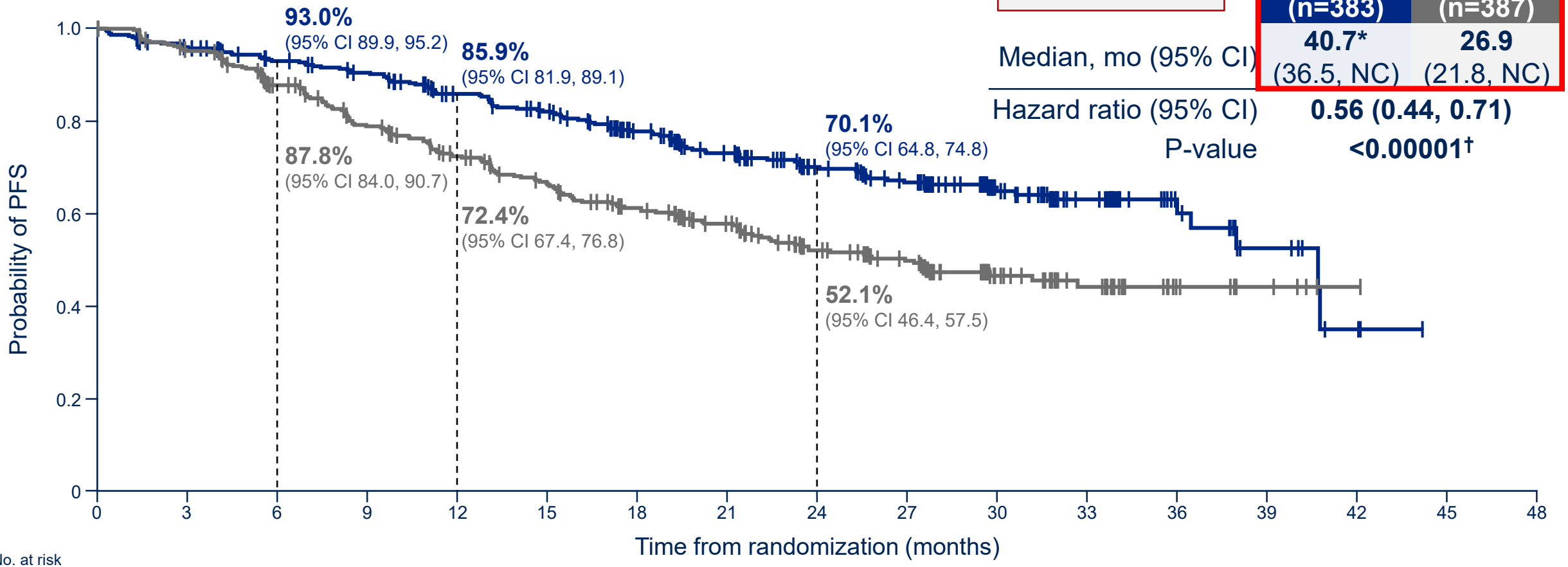
a/mBC, advanced/metastatic breast cancer; BICR, blinded independent central review; DCO, data cutoff; DFI, disease-free interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; HR+/−, hormone receptor–positive/–negative; INV, investigator; mBC, metastatic breast cancer; mets, metastases; mo, months; ORR, objective response rate; OS, overall survival; P, pertuzumab; PFS, progression-free survival; PFS2, second progression-free survival; *PIK3CA*m, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha mutation; Q3W, every 3 weeks; QW, once every week; R, randomization; T-DXd, trastuzumab deruxtecan

NCT04784715. Updated. May 6, 2025. Available from: https://clinicaltrials.gov/study/NCT04784715 (Accessed May 29, 2025)

PFS (BICR): primary endpoint

PFS Δ13.8 mos

	T-DXd + P (n=383)	THP (n=387)
Median, mo (95% CI)	40.7* (36.5, NC)	26.9 (21.8, NC)
Hazard ratio (95% CI)	0.56 (0.44, 0.71)	
P-value	<0.00001†	



No. at risk

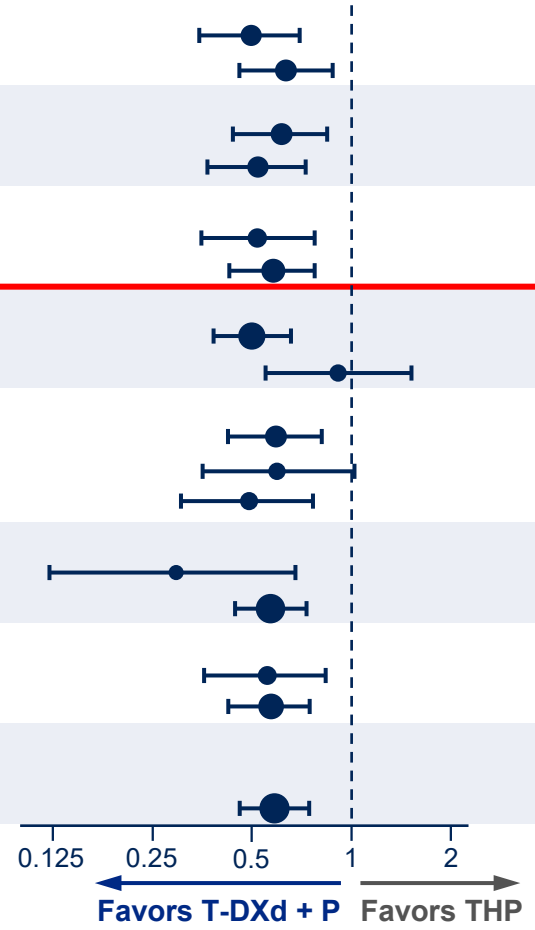
T-DXd + P	383	358	355	321	293	275	242	208	175	153	82	49	21	10	3	0
THP	387	353	312	273	241	215	187	160	124	106	51	32	12	5	1	0

Statistically significant and clinically meaningful PFS benefit with T-DXd + P (median Δ 13.8 mo)

*Median PFS estimate for T-DXd + P is likely to change at updated analysis; †stratified log-rank test. A P-value of <0.00043 was required for interim analysis superiority
BICR, blinded independent central review; CI, confidence interval; mo, months; (m)PFS, (median) progression-free survival; NC, not calculable; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

PFS (BICR): subgroup analyses

	No. of events / no. of patients		mPFS, months (95% CI)		Hazard ratio (95% CI)
	T-DXd + P	THP	T-DXd + P	THP	
Prior treatment status					
De novo	52/200	85/200	NC (36.5, NC)	31.2 (23.5, NC)	0.49 (0.35, 0.70)
Recurrent	66/183	87/187	38.0 (26.9, NC)	22.5 (18.1, NC)	0.63 (0.46, 0.87)
HR status					
Positive	65/207	87/209	38.0 (36.0, NC)	27.7 (22.4, NC)	0.61 (0.44, 0.84)
Negative	53/176	85/178	40.7 (40.7, NC)	22.6 (17.3, 32.7)	0.52 (0.37, 0.73)
***PIK3CA* mutation status**					
Detected	41/116	64/121	36.0 (29.7, NC)	18.1 (15.1, 25.6)	0.52 (0.35, 0.77)
Not detected	76/266	108/266	40.7 (38.0, NC)	32.7 (24.4, NC)	0.57 (0.43, 0.77)
Age at randomization					
<65 years	90/315	139/315	40.7 (36.5, NC)	27.4 (22.4, NC)	0.50 (0.38, 0.65)
≥65 years	28/68	33/72	27.6 (14.9, NC)	21.5 (13.9, NC)	0.92 (0.55, 1.51)
Geographical region					
Asia	62/188	87/191	40.7 (36.5, NC)	27.2 (21.5, NC)	0.60 (0.43, 0.83)
Western Europe and North America	27/87	31/78	36.0 (30.6, NC)	31.2 (15.8, NC)	0.60 (0.35, 1.01)
Rest of World	29/108	54/118	NC (38.0, NC)	24.4 (14.8, NC)	0.48 (0.30, 0.76)
Brain metastases at baseline					
Present	10/25	15/22	31.8 (18.5, NC)	9.5 (5.6, 13.3)	0.30 (0.12, 0.68)
Not present	108/358	157/365	40.7 (36.5, NC)	27.6 (22.6, NC)	0.58 (0.45, 0.74)
Prior exposure to anti-HER2 therapies					
Yes	39/115	51/112	38.0 (26.9, NC)	21.5 (15.3, NC)	0.55 (0.36, 0.83)
No	79/268	121/275	40.7 (36.5, NC)	27.6 (22.5, NC)	0.56 (0.42, 0.74)
Prior exposure to pertuzumab					
Yes	5/31	12/26	40.8 (25.4, NC)	19.8 (7.5, NC)	NC
No	113/352	160/361	40.7 (36.0, NC)	27.4 (22.4, NC)	0.61 (0.48, 0.77)

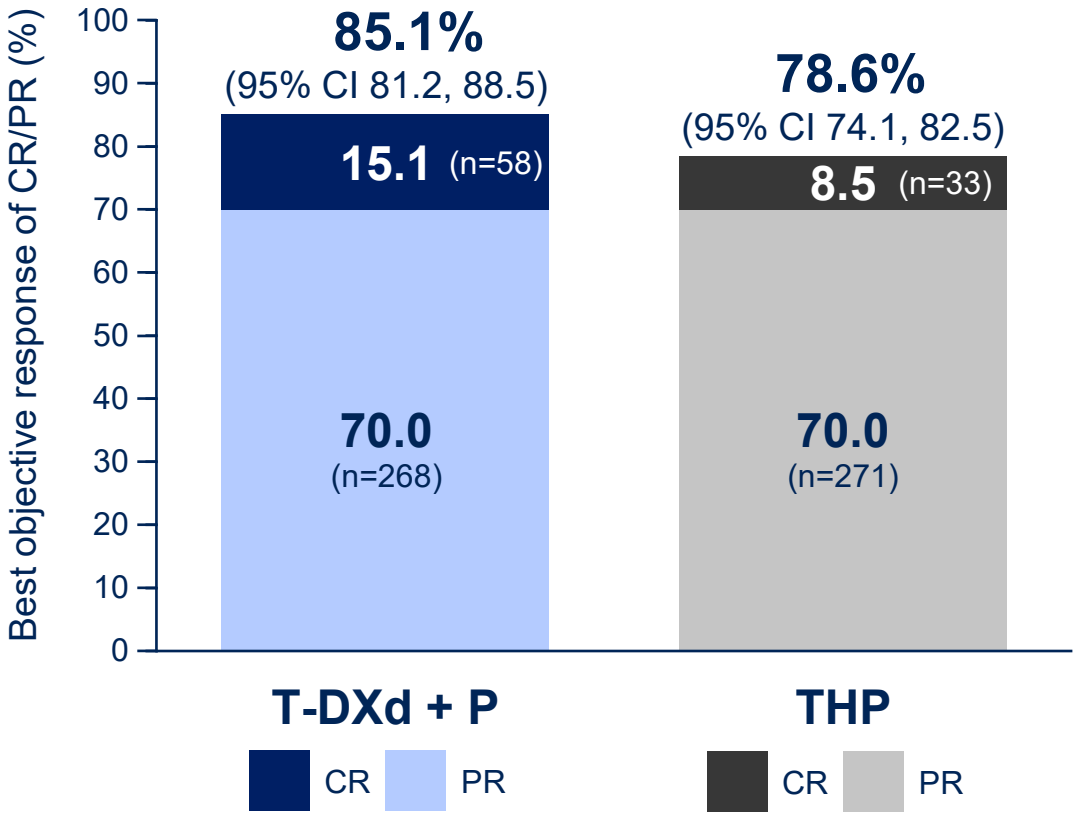


Size of circle is proportional to the number of events
BICR, blinded independent central review;
CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor;
NC, not calculable; P, pertuzumab;
(m)PFS, (median) progression-free survival;
T-DXd, trastuzumab deruxtecan;
THP, taxane + trastuzumab + pertuzumab

PFS benefit with T-DXd + P vs THP was consistently observed across prespecified subgroups, including stratification factors

ORR and DOR (BICR)

Confirmed ORR*

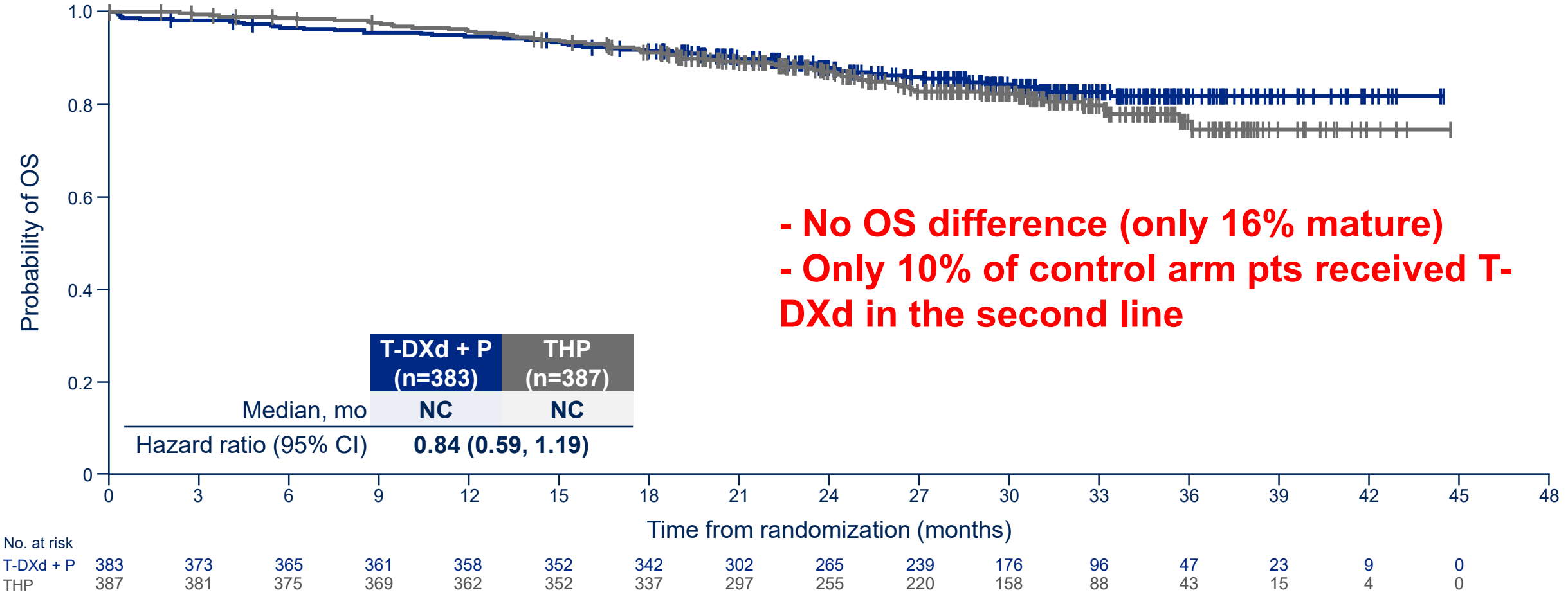


	T-DXd + P (n=383)	THP (n=387)
Median DOR, mo (95% CI)	39.2 (35.1, NC)	26.4 (22.3, NC)
Remaining in response at 24 mo (%)	73.3	54.9
Stable disease, n (%)	38 (9.9)	56 (14.5)

Response rates were greater with T-DXd + P vs THP and were durable

*Based on RECIST v1.1; response required confirmation after 4 weeks
BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; mo, months; NC, not calculable; ORR, objective response rate; P, pertuzumab; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

Overall survival (~16% maturity)



- No OS difference (only 16% mature)
- Only 10% of control arm pts received T-DXd in the second line

Early OS data suggest a positive trend favoring T-DXd + P over THP

CI, confidence interval; OS, overall survival; NC, not calculable; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

DB-09: Toxicity

- T-DXd + P: overall **no unexpected toxicities**
  - 12.1% ILD including 2 (0.5%) deaths
  - LV dysfunction 11% (vs 7.1% THP)
  - TEAEs possibly associated with death 5 (vs 1 with THP)

- Overall **similar incidence of TEAEs across both arms**
  - D/C due to TEAEs: T-DXd 20.8% vs THP 28.3% (Taxane: 25.8%)
  - More dose interruptions/reductions with T-DXd (69% vs 49%; 46% vs 20%)

- During maintenance phase of CLEOPATRA regimen, few side effects and excellent QoL

- Await QoL data from DB-09

DESTINY-Breast12 study design

Phase 3b/4, multicenter, single-arm, two-cohort, open-label study of T-DXd in previously treated HER2+ mBC with and without brain metastases (BMs); the largest prospective study of T-DXd in patients with stable or active BMs

Patient population
- Aged ≥18 years
- Pathologically documented HER2+ advanced or metastatic BC with or without baseline brain metastases
- Received ≤2 prior lines of therapy in the metastatic setting (tucatinib naive)
- Disease progression on prior HER2-directed regimens
- ECOG PS 0 or 1
- No known or suspected leptomeningeal metastases

Baseline brain metastases (N=263)*
- Stable BMs (previously treated)
- Active BMs (untreated or previously treated / progressing [not requiring immediate local therapy])

T-DXd 5.4 mg/kg IV Q3W†

Primary endpoint:
- PFS

Additional endpoints included:
- CNS PFS
- OS
- ORR
- CNS ORR
- Safety and tolerability

No baseline brain metastases (N=241)

T-DXd 5.4 mg/kg IV Q3W†

Primary endpoint:
- ORR

Additional endpoints included:
- OS
- Safety and tolerability

Data reported for the full analysis set (all patients enrolled in the study who received at least one treatment dose) and safety analysis set (identical to full analysis set). No hypothesis testing or comparison of cohorts. Response and progression assessed by ICR per RECIST 1.1 in both cohorts. Patients were enrolled from Australia, Canada, Europe, Japan, and United States
*Concomitant use of ≤3 mg of dexamethasone daily or equivalent allowed for symptom control of BMs (baseline BMs cohort only); †until RECIST 1.1-defined disease progression outside the CNS
BC, breast cancer; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; ICR, independent central review; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan
NCT04739761. Updated. July 19, 2024. Available from: https://www.clinicaltrials.gov/study/NCT04739761 (Accessed September 9, 2024)

Outcomes for CNS and non-CNS pts similar:

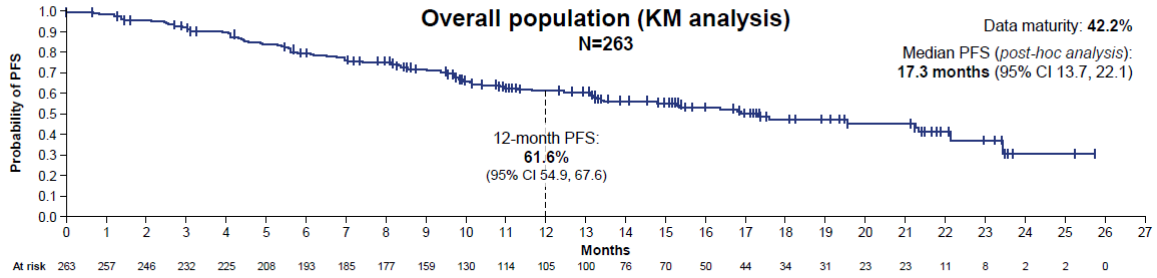
PFS at 12 months = 61.6%

CNS PFS at 12 months = 58.9%

ORR (all) = 64.1%

CNS ORR = 71.7%

Baseline BMs: PFS (primary endpoint)

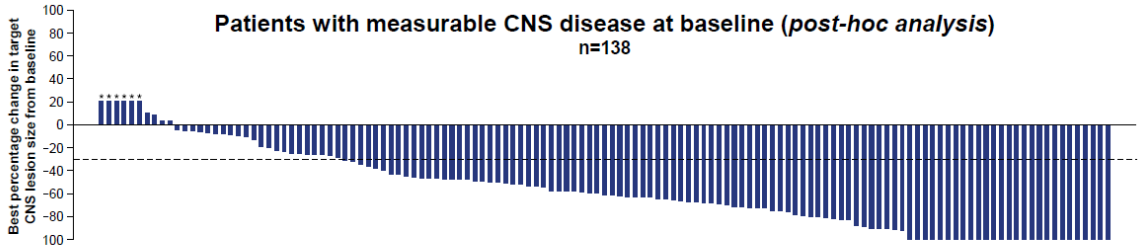


	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)	Active BM subgroups: Untreated (n=39) Post-hoc analysis	Active BM subgroups: Previously treated / progressing (n=67) Post-hoc analysis
Overall no. events	111	64	47	20	27
12-month PFS, % (95% CI)	61.6 (54.9, 67.6)	62.9 (54.0, 70.5)	59.6 (49.0, 68.7)	47.0 (29.6, 62.7)	66.7 (53.4, 76.9)

T-DXd showed consistent 12-month PFS in patients with stable and active BMs

PFS assessed by ICR per RECIST 1.1
BM, brain metastasis; CI, confidence interval; ICR, independent central review; KM, Kaplan-Meier; no., number of; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

Baseline BMs: CNS ORR



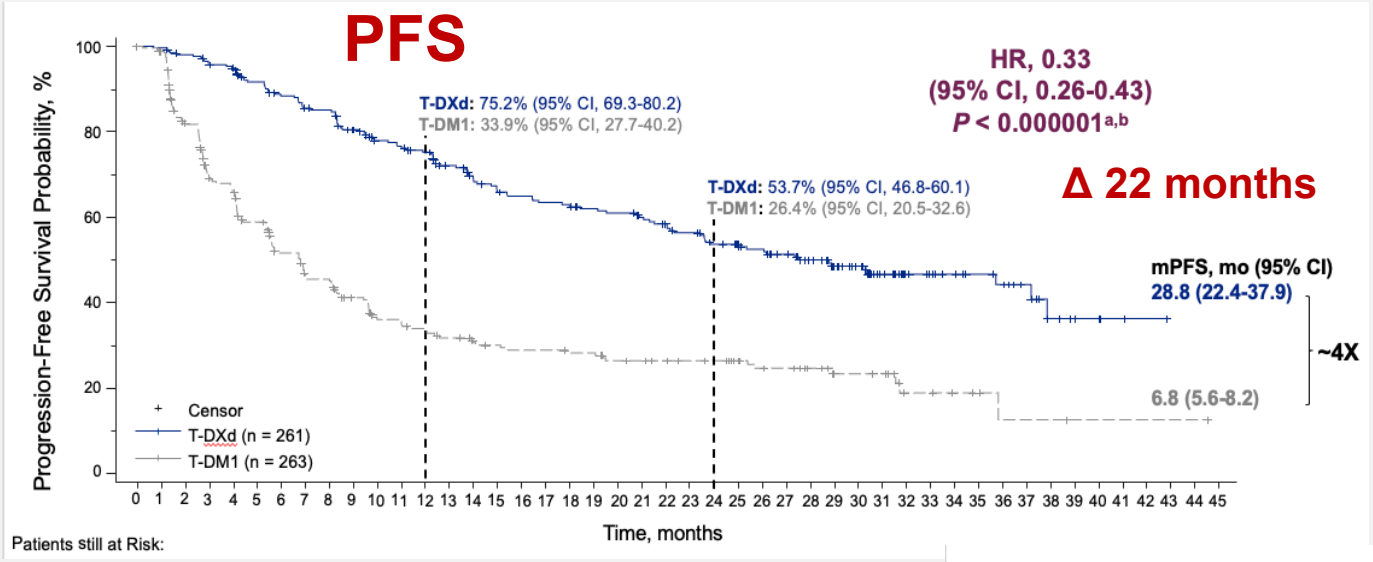
Measurable CNS disease at baseline	All patients (n=138)	Stable BMs (n=77)	Active BMs (n=61)	Active BM subgroups: Untreated (n=23) Post-hoc analysis	Active BM subgroups: Previously treated / progressing (n=38) Post-hoc analysis
Confirmed CNS ORR, % (95% CI)	71.7 (64.2, 79.3)	79.2 (70.2, 88.3)	62.3 (50.1, 74.5)	82.6 (67.1, 98.1)	50.0 (34.1, 65.9)

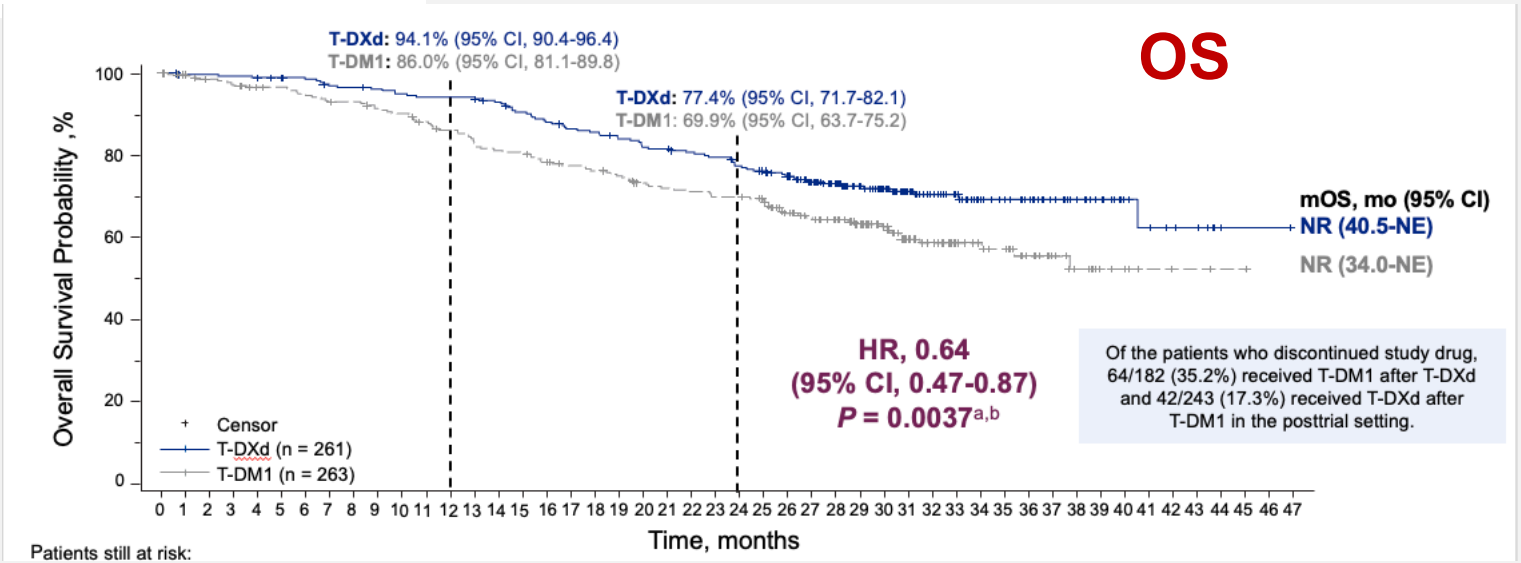
T-DXd showed substantial CNS responses in the overall BMs population, including patients with stable and active BMs

Lin N et al. ESMO, 2024.

Slide courtesy of Sarah Sammons MD

T-DXd improves PFS and OS in 2nd line HER2+ MBC (Destiny-Breast03)



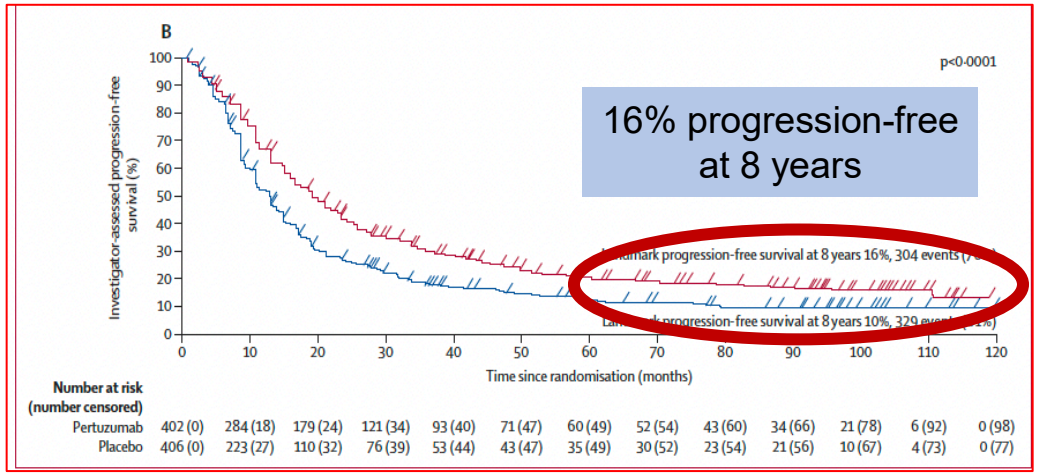


Slightly modified from:
PRESENTED BY: Claudine Isaacs, MD, FRCPC

Hurvitz S. SABCS 2022; GS2-02; Lancet Oncol 2023; 401:105-17
Cortez J et al. Nature Med 2024;30:2208-15

How Do We Best Sequence HER2 Directed Therapy?

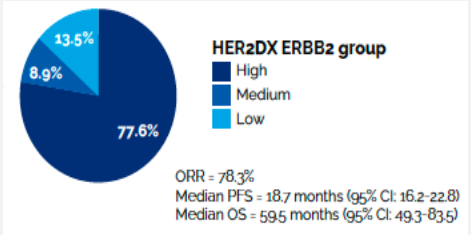
Markers of long-term response on THP

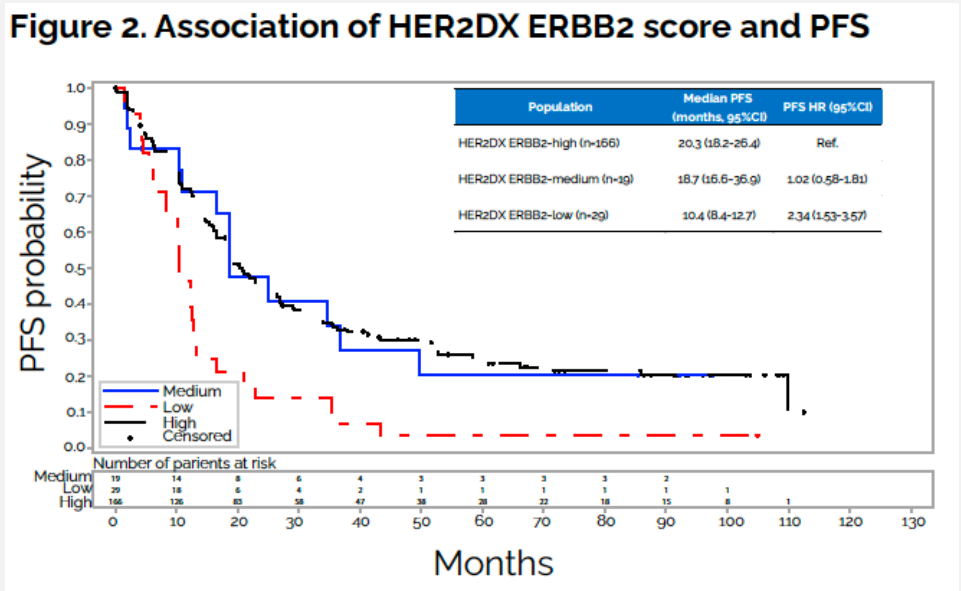


Long-term (≥ 3 yrs) response more common:

- de novo mBC
- longer DFI
- non visceral disease
- IHC3+/High *HER2* mRNA, low serum HER2
- *PIK3CAwt*

HER2DX assay performed on ~ 50% of patients randomized to THP in CLEOPATRA





PRESENTED BY: Claudine Isaacs, MD, FRCPC

Swain S et al. *Lancet Oncol* 2020; 21: 519-30
Cortes J et al. SABCS 2024; PS4-06

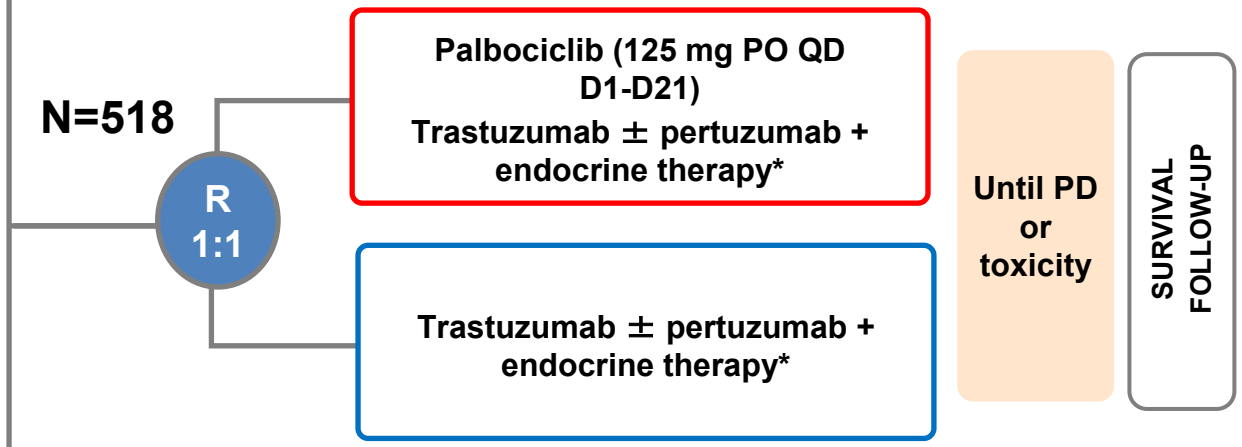
AFT-38 PATINA Study Design

Registration

- Histologically confirmed HR+,HER2+ mBC
- No prior treatment in the advanced setting beyond induction treatment
- 6-8 cycles of treatment, including trastuzumab ± pertuzumab and taxane/vinorelbine

Key eligibility criteria

- Completion of induction chemotherapy and no evidence of disease progression (i.e., CR, PR, or SD)

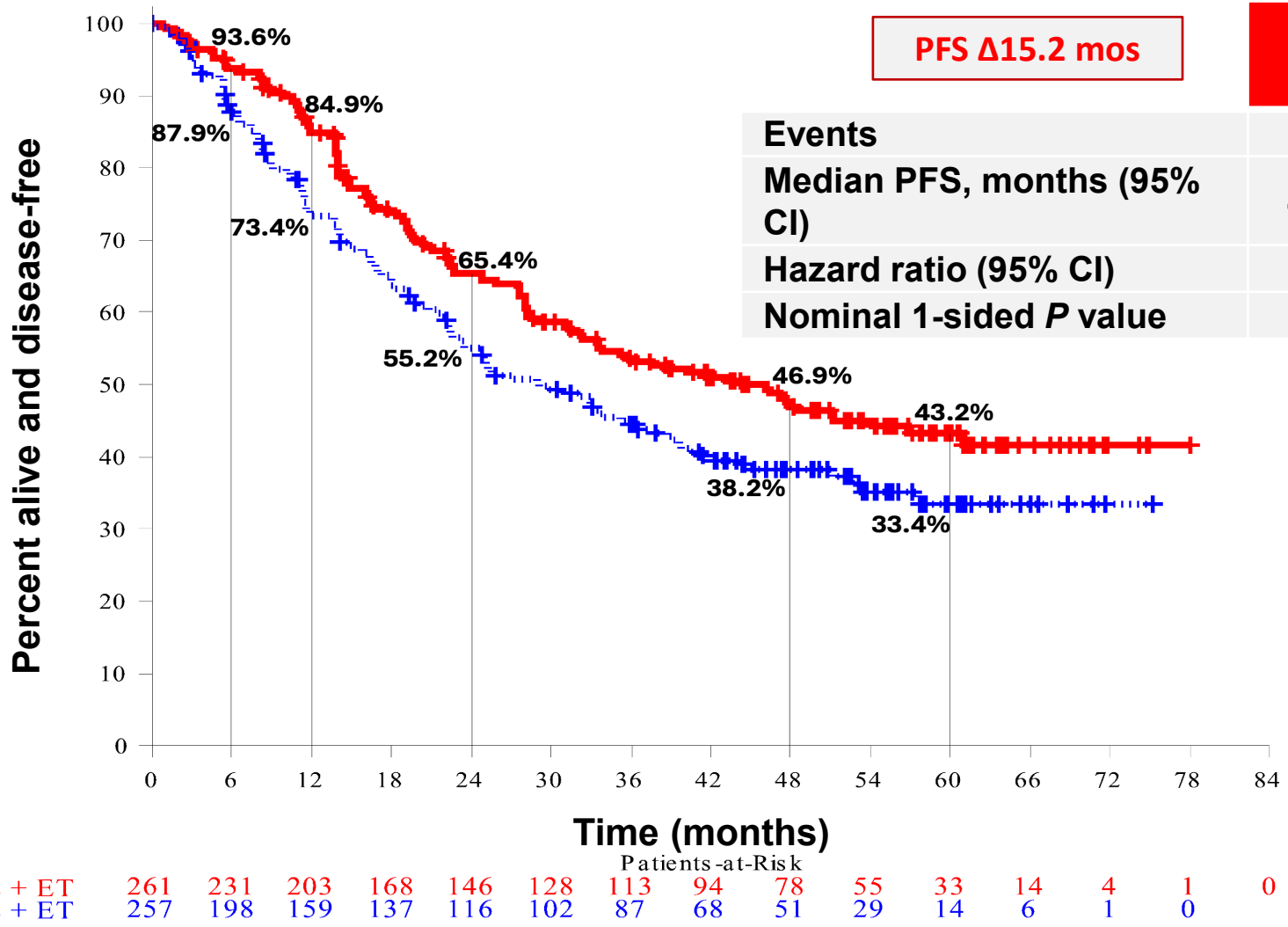


Stratification factors

- Pertuzumab use (yes vs no)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs no, including de novo)†
- Response to induction therapy (CR or PR vs SD) by investigator assessment†
- Type of endocrine therapy (fulvestrant vs aromatase inhibitor)

*Trastuzumab and pertuzumab were administered per SOC. Endocrine therapy options include an aromatase inhibitor or fulvestrant. †Factors used in stratified analyses.
CR=complete response; D=day; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mBC=metastatic breast cancer; PD=progressive disease; PO=orally; PR=partial response; QD=once a day; R=randomization; SD=stable disease; SOC=standard of care.

Primary Endpoint: PFS (Investigator-Assessed)



PFS Δ15.2 mos

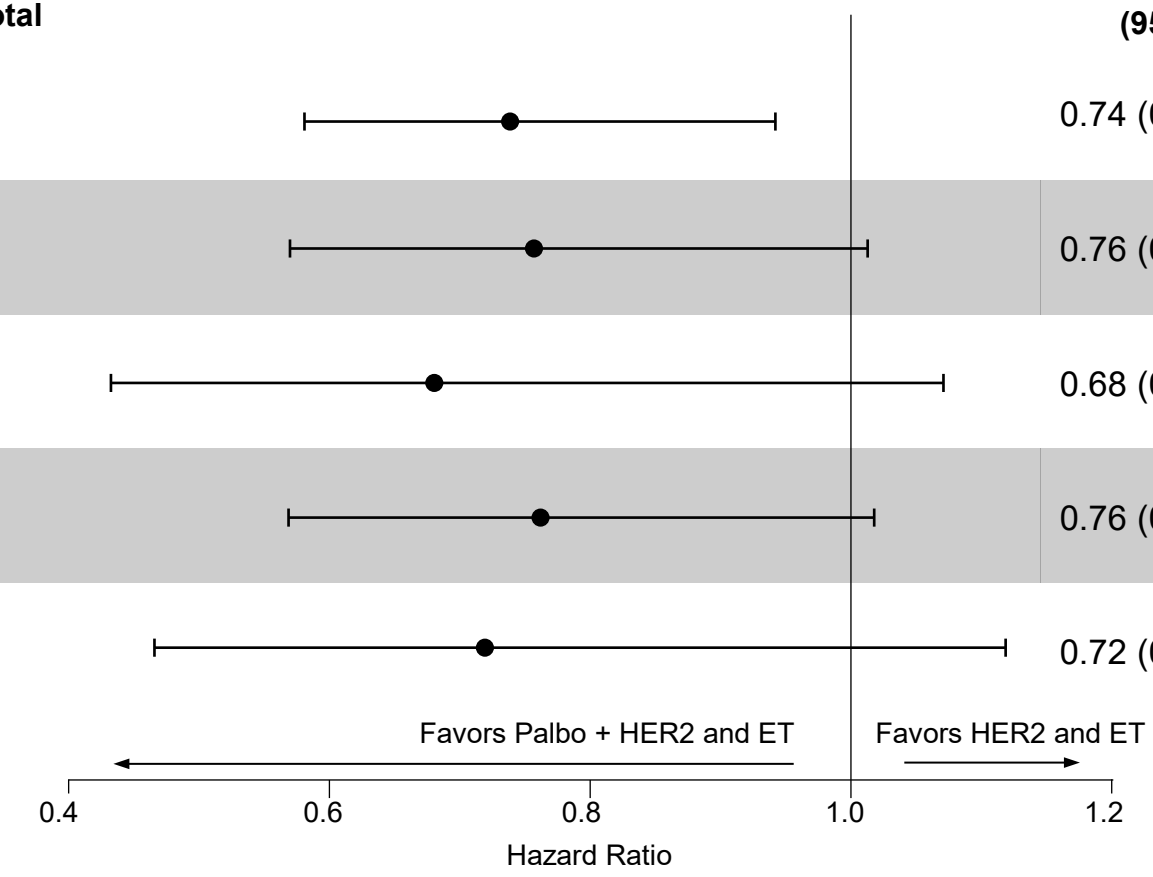
	Palbo + anti-HER2 and ET	Anti-HER2 and ET
Events	126/261	136/257
Median PFS, months (95% CI)	**44.3** (32.4-60.9)	**29.1** (23.3-38.6)
Hazard ratio (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided *P* value	0.0074	

Median follow-up on patients who are alive and disease-free, 52.6 months

CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; palbo=palbociclib.

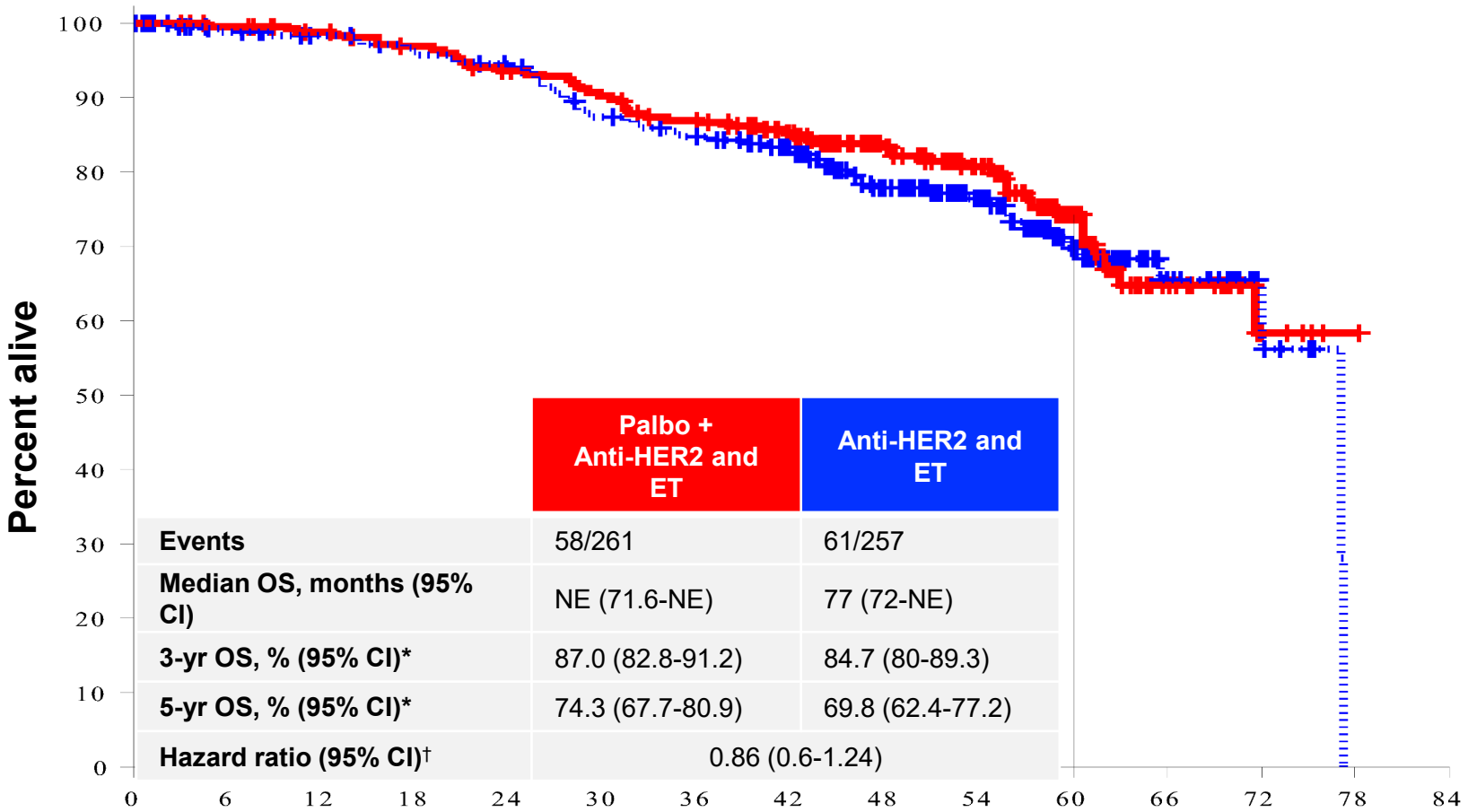
PFS by Stratification Subgroups

	Events/Total	Hazard Ratio (95% CI)
Overall	262/518	0.74 (0.58-0.94)
Prior anti-HER2 therapy	186/372	0.76 (0.57-1.01)
No prior anti-HER2 therapy	76/146	0.68 (0.543-1.07)
Best response to induction (CR* or PR*)	182/355	0.76 (0.57-1.02)
Best response to induction (SD*)	80/163	0.72 (0.47-1.12)



*Factors used in stratified analyses.
CR=Complete Response; Palbo=palbociclib; PR=Partial Response; SD=Stable Disease

Secondary Endpoint: Overall Survival (Interim Analysis)



	Palbo + Anti-HER2 and ET	Anti-HER2 and ET
Events	58/261	61/257
Median OS, months (95% CI)	NE (71.6-NE)	77 (72-NE)
3-yr OS, % (95% CI)*	87.0 (82.8-91.2)	84.7 (80-89.3)
5-yr OS, % (95% CI)*	74.3 (67.7-80.9)	69.8 (62.4-77.2)
Hazard ratio (95% CI)†	0.86 (0.6-1.24)	

Patients-at-Risk

Palbo + HER2 + ET	261	255	248	239	229	220	207	187	146	101	60	22	7	1	0
HER2 + ET	257	235	228	221	215	197	188	167	125	90	49	22	6	0	

*Kaplan-Meier method.
†Unstratified Cox model.
CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; NE=not evaluable; OS=overall survival; palbo=palbociclib.

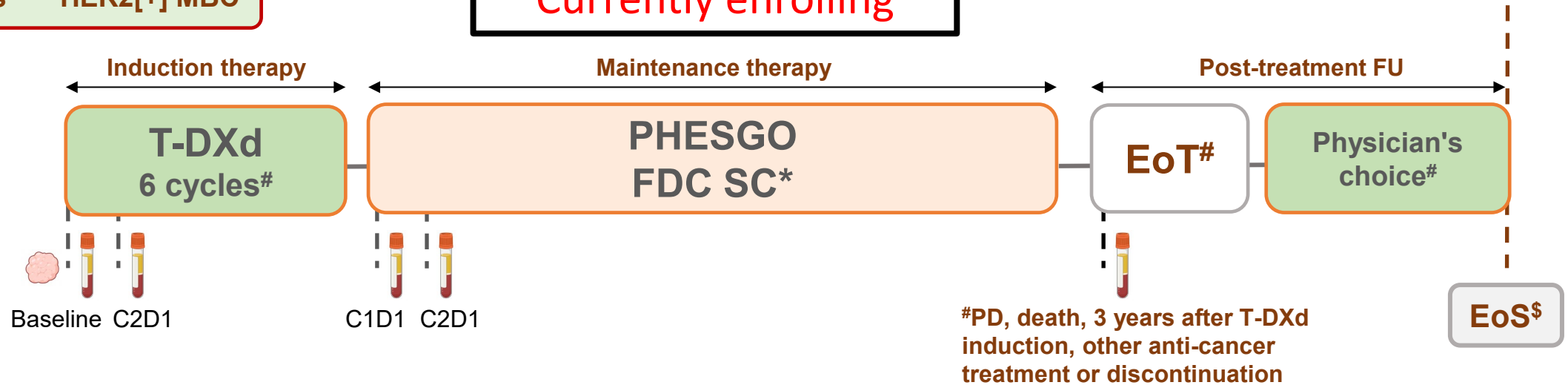
T-DXd induction: The best of both worlds?
The DEMETHER Study

MEDSIR
MEDICA SCIENTIA INNOVATION RESEARCH

Study Design

165 patients **HER2[+] MBC**

Currently enrolling



Treatment regimen:

- **T-DXd**: 5.4 mg/kg; IV, Q3W - 6 cycles.

  #T-DXd is allowed upon progression on PHESGO.
- **PHESGO FDC SC**: 1200 mg pertuzumab, 600 mg trastuzumab (LD) - 600 mg pertuzumab, 600 mg trastuzumab; Q3W.

  *Additional HT will be administered in the maintenance phase to patients with confirmed HR[+] status.

$All patients will be followed up until 36 months + 28 days (± 7 days) after T-DXd initiation of LPI, unless premature study termination.

EoS: end of study; **EoT**: end of treatment; **ET**: endocrine therapy; **FDC:** fixed dose combination; **FU:** follow up; **HER2:** Human Epidermal Growth Factor Receptor 2; **HR[+]:** hormone receptor-positive; **HT**: hormone therapy; **IV:** intravenously; **LD:** loading dose; **LPI**: last patient in; **MBC:** metastatic breast cancer; **PD:** progressive disease; **Q3W:** every 3 weeks; **SC**: subcutaneously; **T-DXd:** trastuzumab deruxtecan.

Case

- 52 yo F presents with cT3N1 HR- HER2+ metastatic breast cancer
- Staging scans reveal multiple 5-10 mm lung nodules and two 1.5 cm liver lesions (all asymptomatic)
- Biopsy of one liver lesion shows metastatic HR- HER2+ metastatic breast cancer (HER2 IHC 3+)
- ***What first-line therapy do you recommend for this patient?***

Case

- 52 yo F presents with cT3N1 HR+ HER2+ metastatic breast cancer
- Staging scans reveal multiple bone lesions and two 1.5 cm liver lesions (all asymptomatic)
- Biopsy of one liver lesion shows metastatic HR+ HER2+ metastatic breast cancer (HER2 IHC 3+)
- ***What first-line therapy do you recommend for this patient?***

Case

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- Staging scans reveal multiple bone lesions and two 1.5 cm liver lesions (all asymptomatic)
- Biopsy of one liver lesion shows metastatic HR+ HER2+ metastatic breast cancer (HER2 IHC 3+)
- She reports headaches – brain MRI shows two 7-8 mm lesions consistent with brain metastases
- She undergoes SRS to each of the two brain metastases
- ***What first-line therapy do you recommend for this patient?***

Case

- 38 yo F originally presented with cT2N1 HR+ HER2+ early-stage breast cancer (negative staging scans at initial diagnosis)
- Neoadjuvant TCHP → ypT1cN1 (RCB III) – minimal response
- Receives adjuvant T-DM1, ovarian suppression, aromatase inhibitor
- 4 months after completing adjuvant T-DM1, she reports back pain
- Staging scans now show innumerable bony metastases
- Biopsy of bony lesion = HR+ HER2+ metastatic breast cancer
- ***What systemic therapy do you recommend for this patient?***

Outline

- Selection of first-line therapy for **HER2+ metastatic breast cancer**
- Selection of first-line cytotoxic treatment for endocrine-refractory **HR+ HER2 low/ultralow metastatic breast cancer**

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)

60% capecitabine
24% nab-paclitaxel
16% 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)

Modified from G Curigliano et al ASCO 2024

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

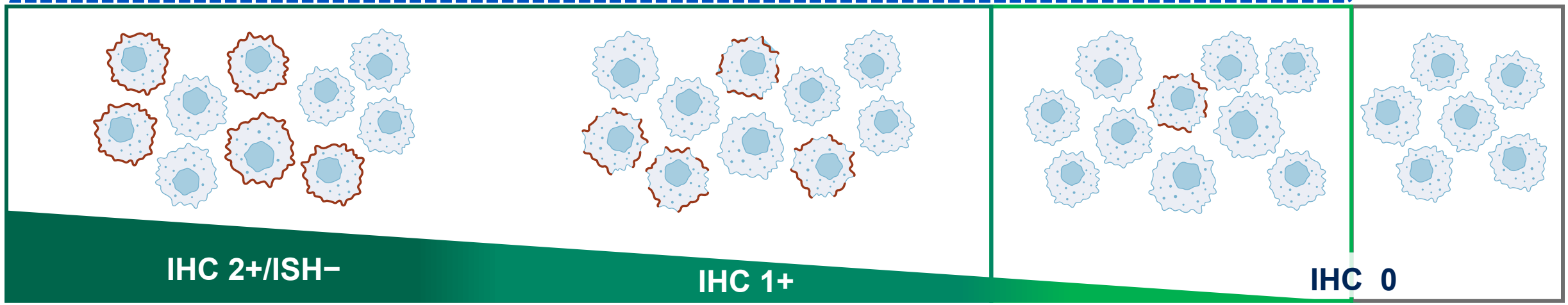
HER2 IHC categories within HR+, HER2-negative (HER2−) mBC (per ASCO/CAP[1])

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

HER2-low ~60–65%[2,3]

HER2-ultralow ~20–25%[2–4]

HER2 null ~10-20%

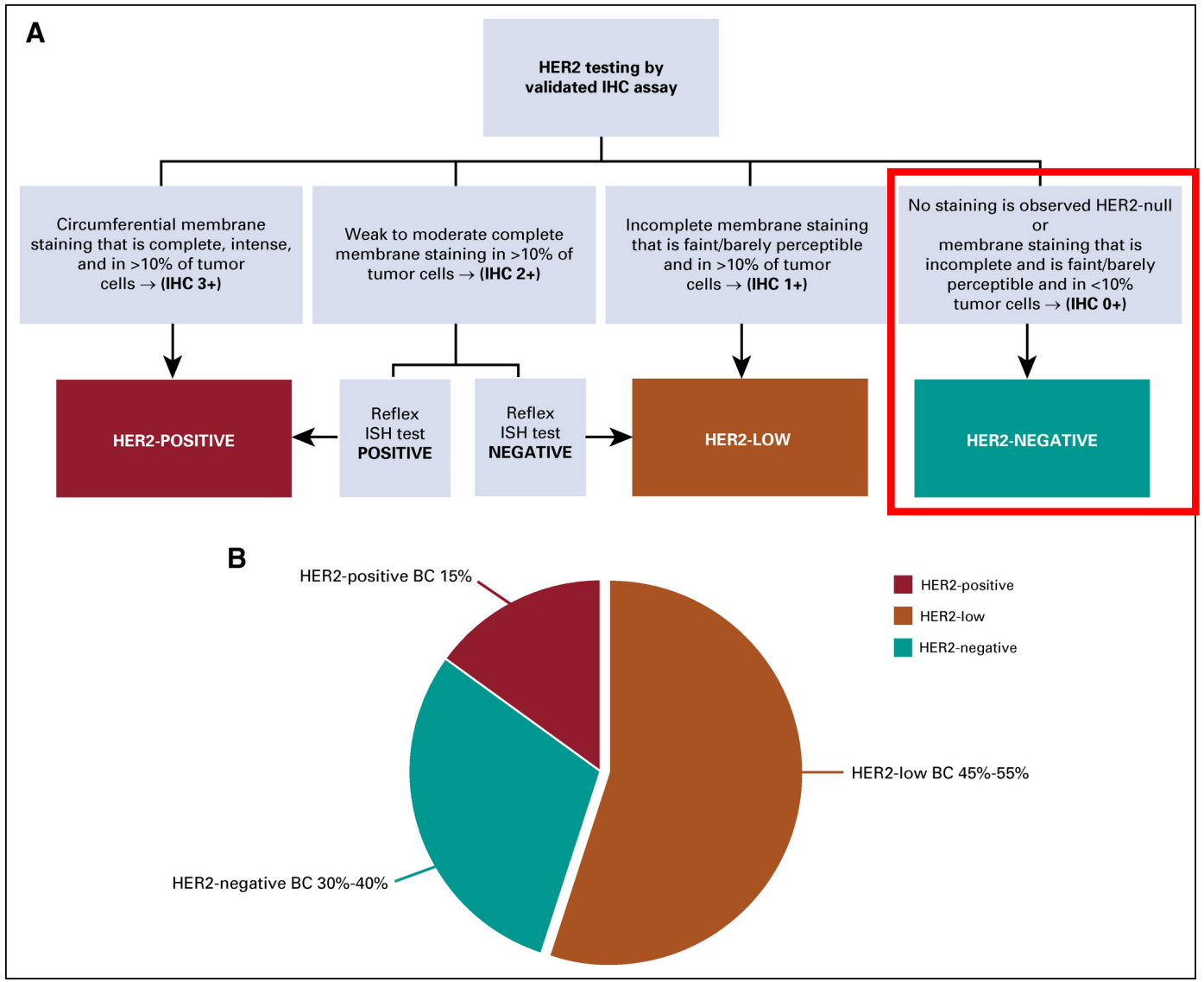


IHC 2+/ISH−	IHC 1+	IHC 0	HER2 null
Weak-to-moderate complete membrane staining in >10% tumor cells	Faint, incomplete membrane staining in >10% tumor cells	**Faint, incomplete membrane staining in ≤10% tumor cells**	Absent / no observable membrane staining

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

Expanding HER2 categories: positive, low, ultralow (0+), null (0)



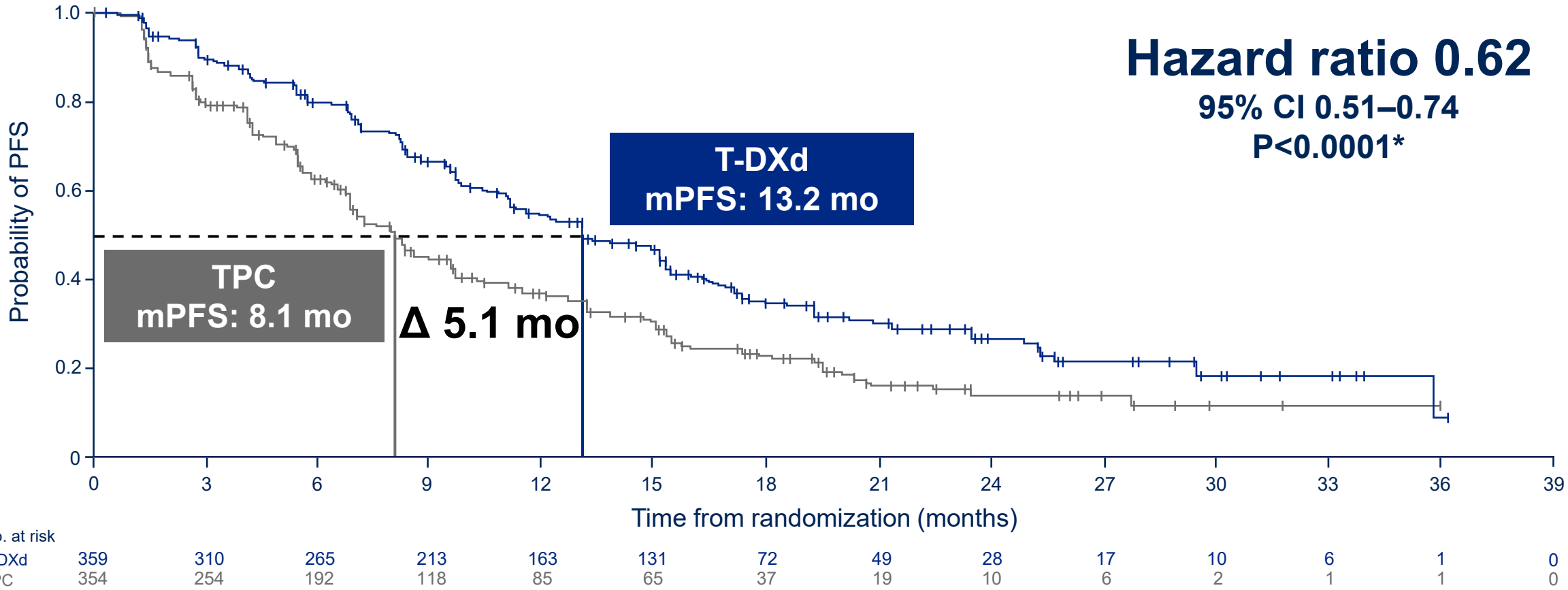
2025:

HER2 null:
IHC 0 (0% expression)

HER2 ultralow:
IHC 0+ (1-10% expression)

Tarantino P et al. J Clin Oncol. 2020

PFS (BICR) in HER2-low: primary endpoint

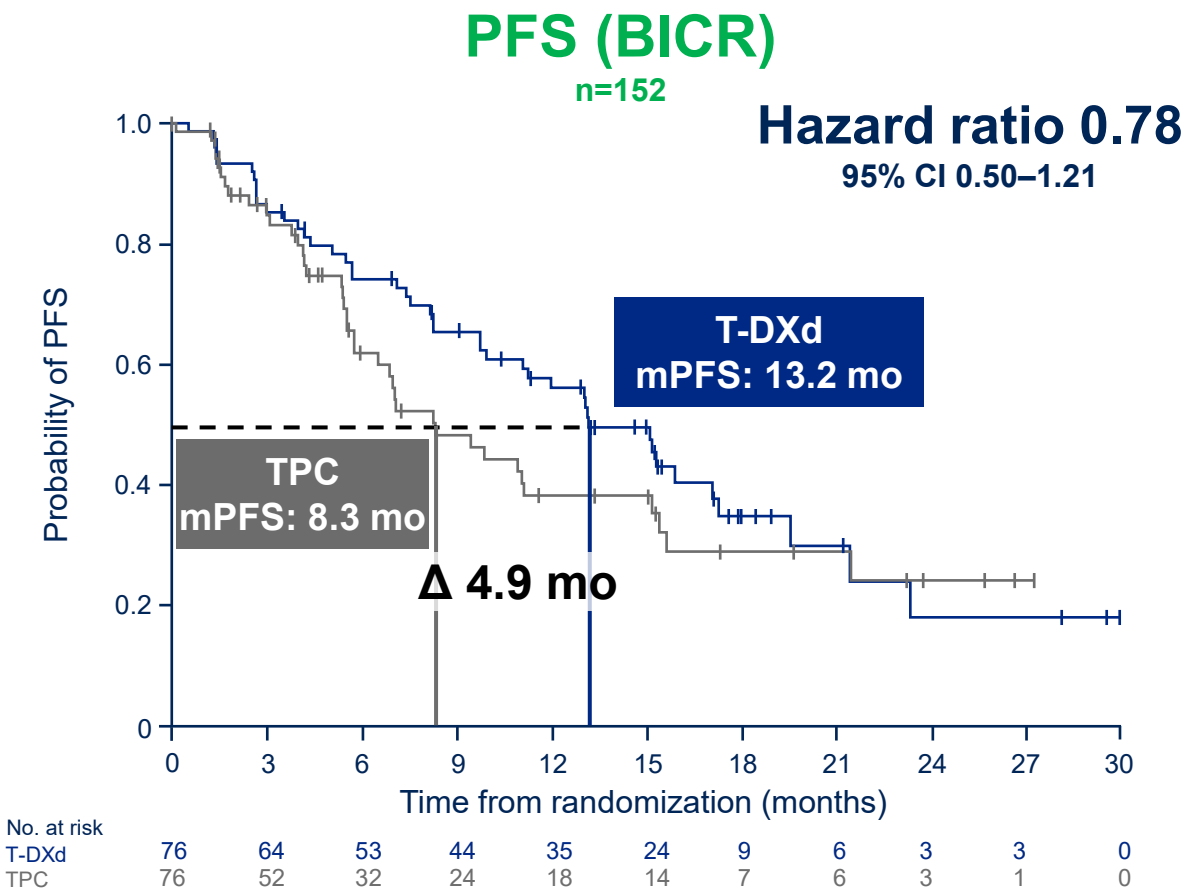


T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance

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

PFS in HER2-ultralow: prespecified exploratory analyses



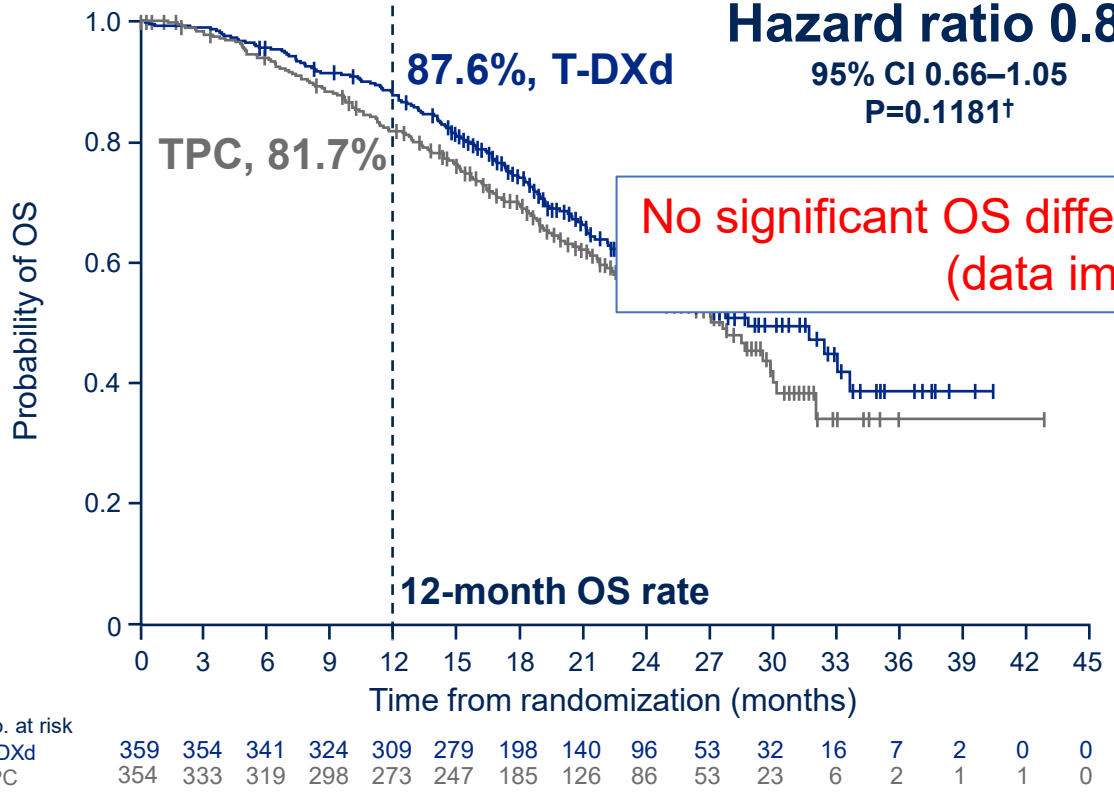
PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*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

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

HER2-low*

n=713



No. at risk

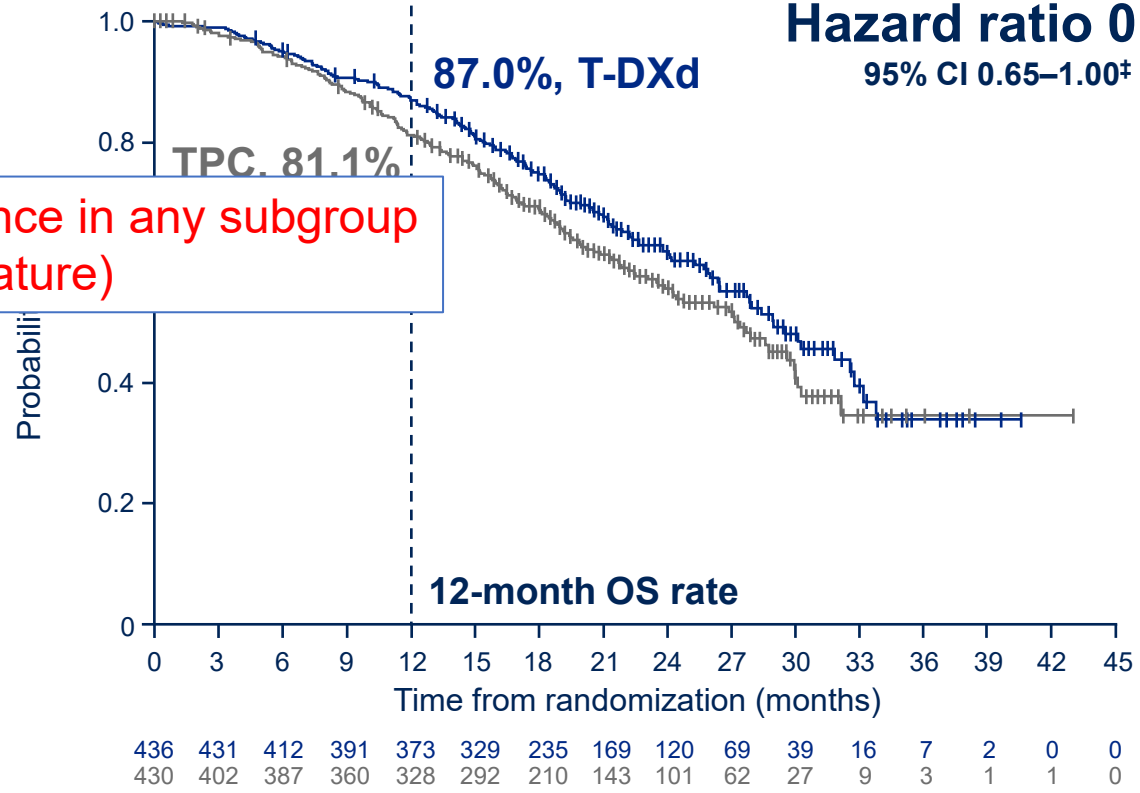
T-DXd	359	354	341	324	309	279	198	140	96	53	32	16	7	2	0	0
TPC	354	333	319	298	273	247	185	126	86	53	23	6	2	1	1	0

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

No significant OS difference in any subgroup (data immature)

ITT (HER2-low + HER2-ultralow)

N=866



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

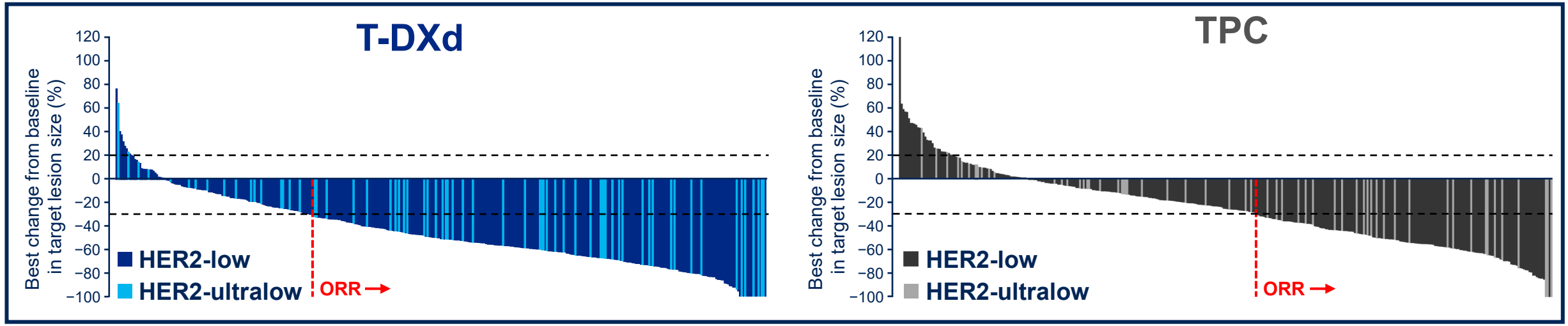
17.9% of patients in the TPC group received T-DXd post treatment discontinuation (ITT)

*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

Antitumor activity

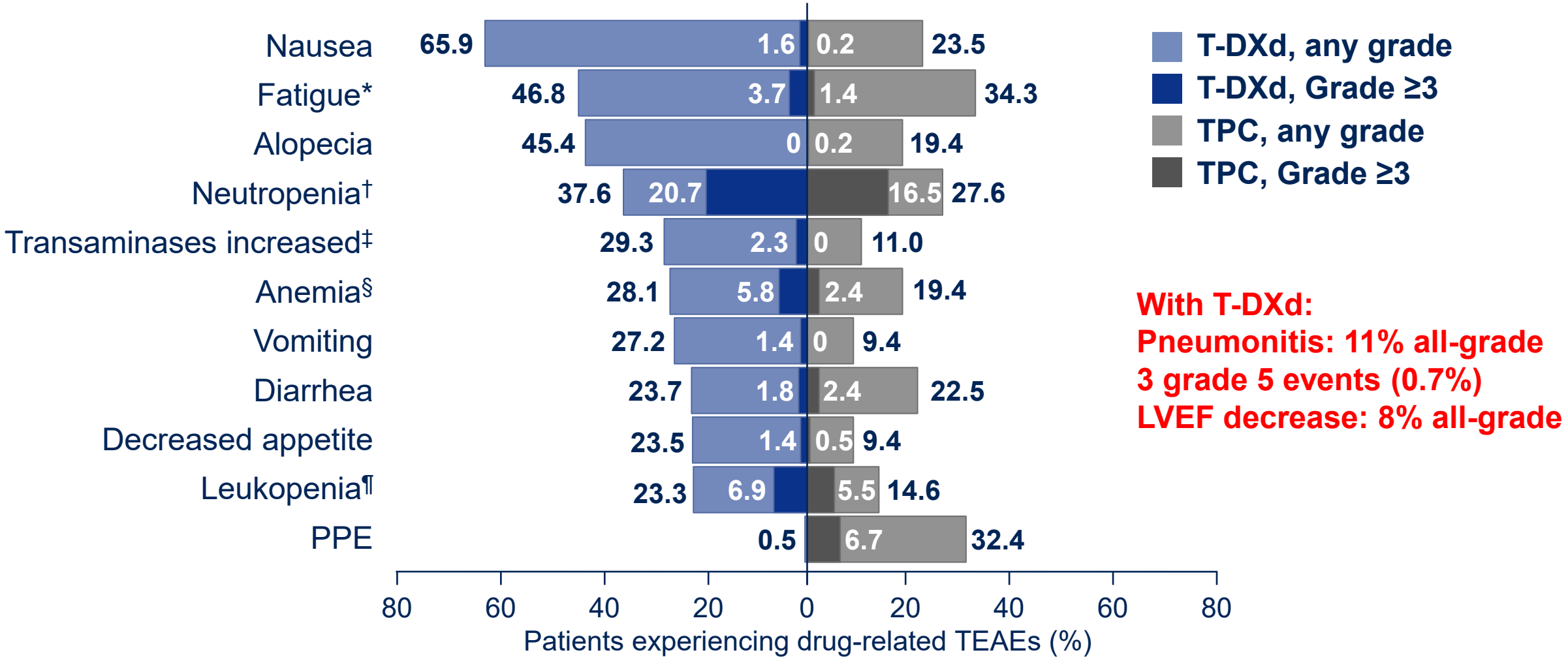
Time to response: ~2.7 mos in both arms



	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

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



With T-DXd:
Pneumonitis: 11% all-grade
3 grade 5 events (0.7%)
LVEF decrease: 8% all-grade

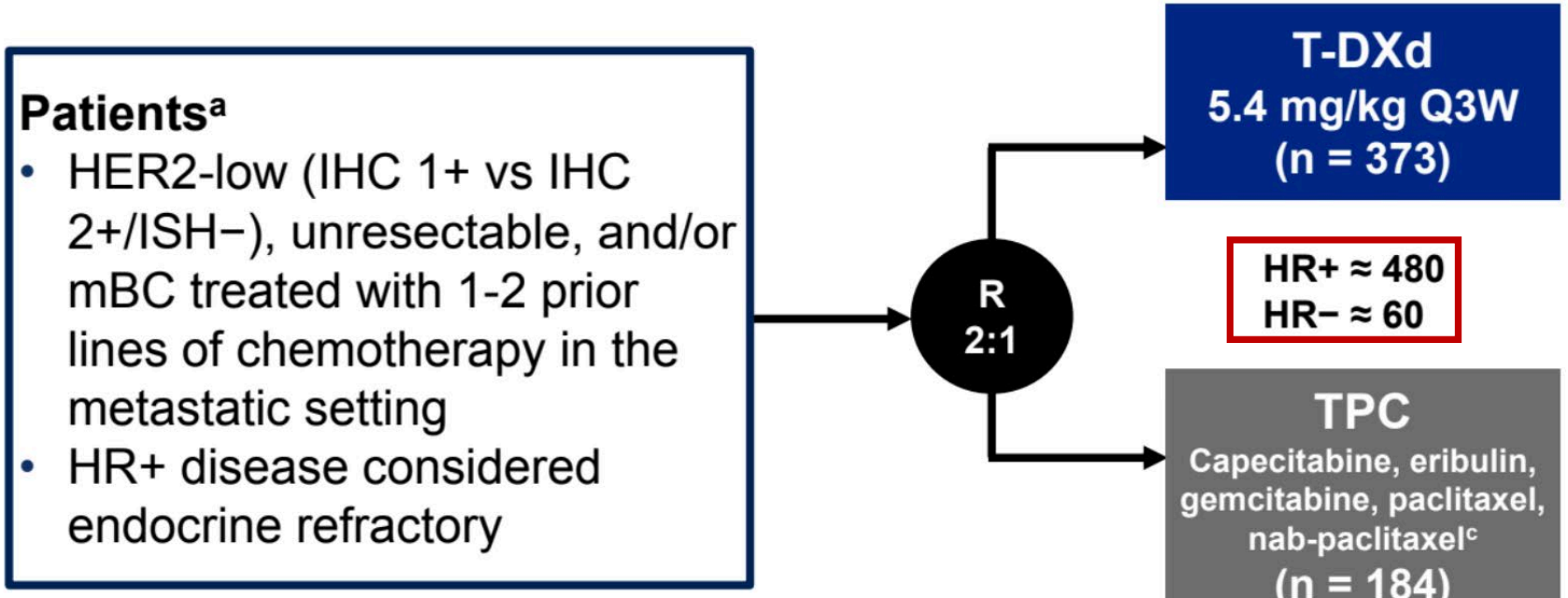
*Includes the preferred terms fatigue, asthenia, malaise, and lethargy; †includes the preferred terms neutrophil count decreased and neutropenia; ‡includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase 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

NCCN 1/2025: Endocrine-refractory HR+ MBC

SYSTEMIC THERAPY FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory		
See BINV-Q (1) for Considerations for Systemic Therapy.		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b] and/or IHC HER2 0+, 1+, or 2+/ISH negative[d]	Systemic chemotherapy[e] (category 1, preferred) BINV-Q (5), or fam-trastuzumab deruxtecan-nxki[e,f] (other recommended regimen)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	HER2 IHC 0+, 1+, or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[f] (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan-nxki	Sacituzumab govitecan[g] (Category 1, preferred)
		Systemic chemotherapy BINV-Q (5)
		Targeted therapy BINV-Q (6) and BINV-Q (7)
		For HER2 IHC 0, 1+, or 2+/ISH negative:[d] Datopotamab deruxtecan-dlnk[h] (other recommended regimen)
Third Line and beyond	Any	Systemic chemotherapy BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents and emerging biomarker options BINV-Q (6), BINV-Q (7), and BINV-Q (8)

PHASE 3 trial: DESTINY-Breast04



Primary endpoint

- PFS by BICR (HR+)

Key secondary endpoints[b]

- PFS by BICR (all patients)
- OS (HR+ and all patients)

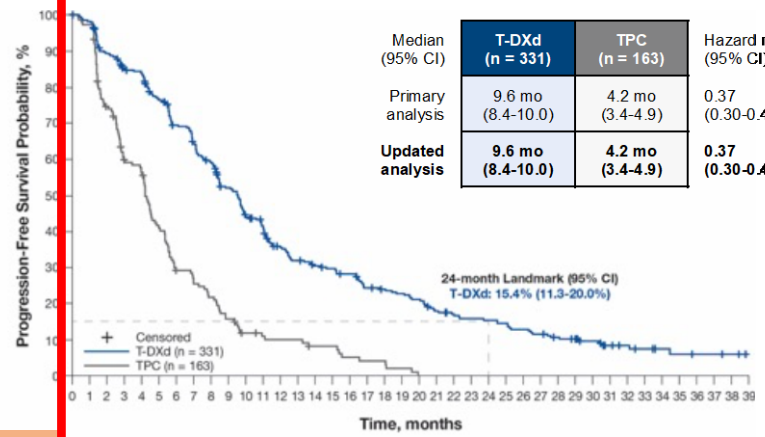
Stratification factors

- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

DB04: Trastuzumab deruxtecan in HER2-low MBC

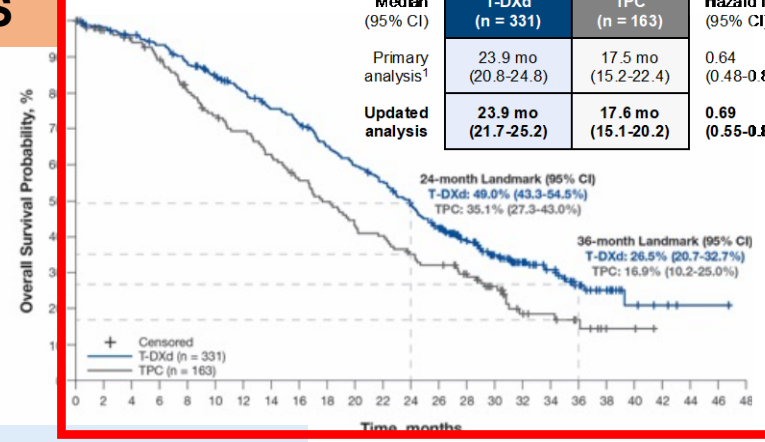
Hormone Receptor-positive (n=494)

PFS



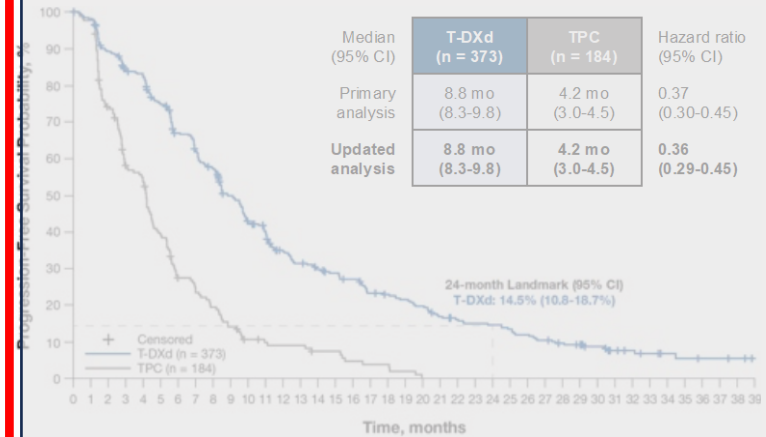
	Median (95% CI) T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**

OS

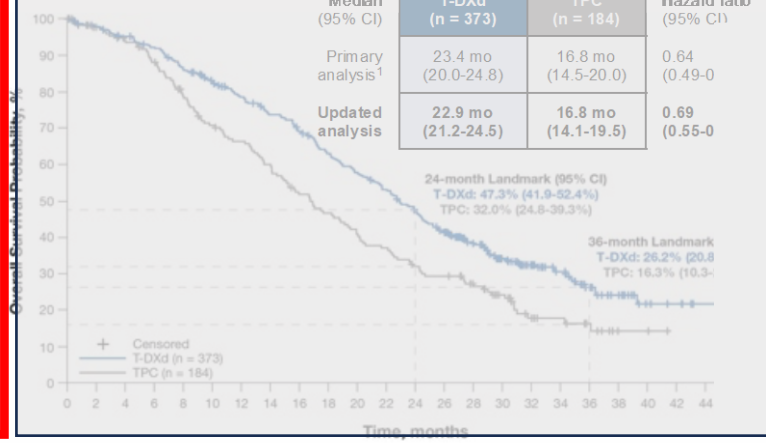


	Median (95% CI) T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**

ALL Patients (n=557)

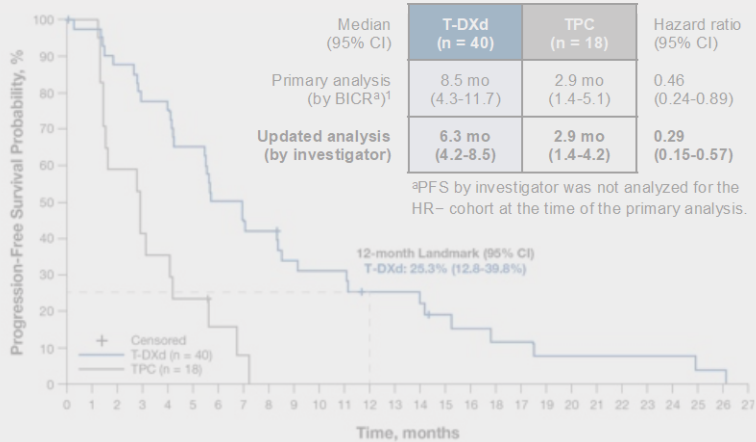


	Median (95% CI) T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**



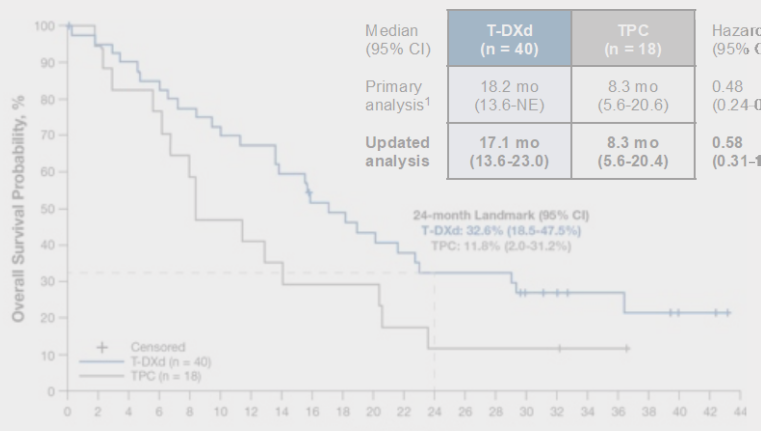
	Median (95% CI) T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[1]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0**

Hormone Receptor-negative (n=58)



	Median (95% CI) T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.



	Median (95% CI) T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.96)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**

Median FU: 32.0 months

Modi S et al. ESMO 2023.

PRESENTED BY: Ana C. Garrido-Castro, M.D.

Case

- 58 yo F with metastatic HR+/HER2 ultralow breast cancer and *PIK3CA* mutation
- No relevant comorbidities, labs WNL, compliant with all recommended treatments
- Treatment so far:
  - Letrozole + ribociclib – 24 mos, stopped for progression
  - Fulvestrant + capivasertib – 7 mos, stopped for progression
- Current disease burden = “innumerable” bony mets, two 1.5 cm liver lesions (all asymptomatic)
- ***What is the next therapy you recommend for this patient?***

Case

- 58 yo F with metastatic HR+/HER2 ultralow breast cancer and *PIK3CA* mutation
- No relevant comorbidities, labs WNL, compliant with all recommended treatments
- Treatment so far:
  - Letrozole + ribociclib – 24 mos, stopped for progression
  - Fulvestrant + capivasertib – 7 mos, stopped for progression
- Current disease burden = “innumerable” bony mets, two 1.5 cm liver lesions + low back and hip pain due to mets
- ***What is the next therapy you recommend for this patient?***

Case

- 47 yo F with metastatic HR+/HER2 low breast cancer
- Originally diagnosed with stage II HR+/HER2- disease 3 yrs ago – at the time, received neoadjuvant ddAC-T, then adjuvant ovarian suppression + letrozole → mets to lung + bones
- Started on fulvestrant + ribociclib – progressed after 10 months with new asymptomatic liver mets and 3 sub-centimeter brain mets (symptomatic with headaches, dizziness)
- Underwent SRS x3 to all brain mets, with good outcome
- ***What is the next therapy you recommend for this patient?***

THANK YOU!