SESSIONE I – Focus on…

Il carcinoma mammario metastatico HER2 low: i cambiamenti nel paradigma terapeutico

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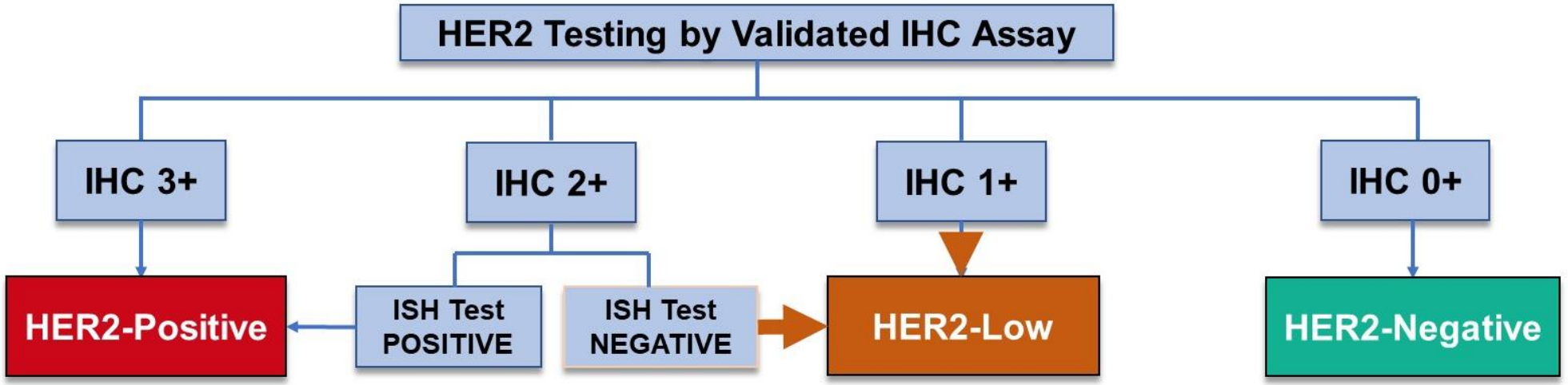
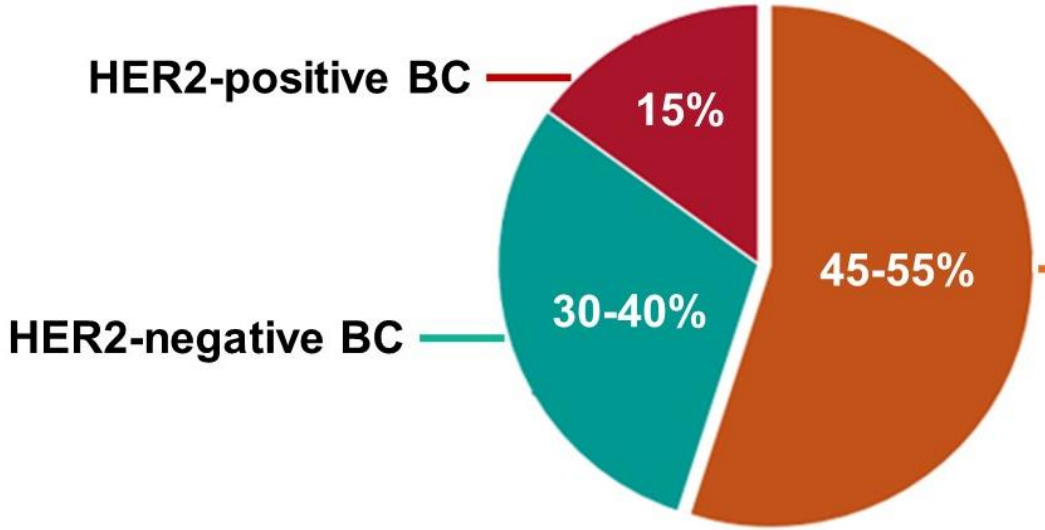
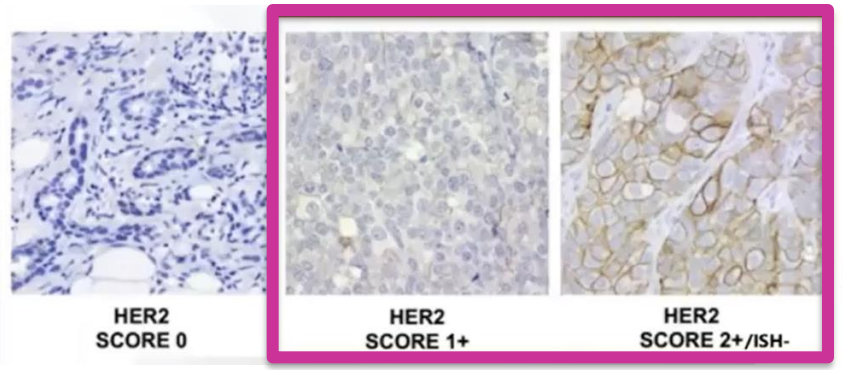
Roma, 11 Ottobre 2024

HER2-low BC Definition





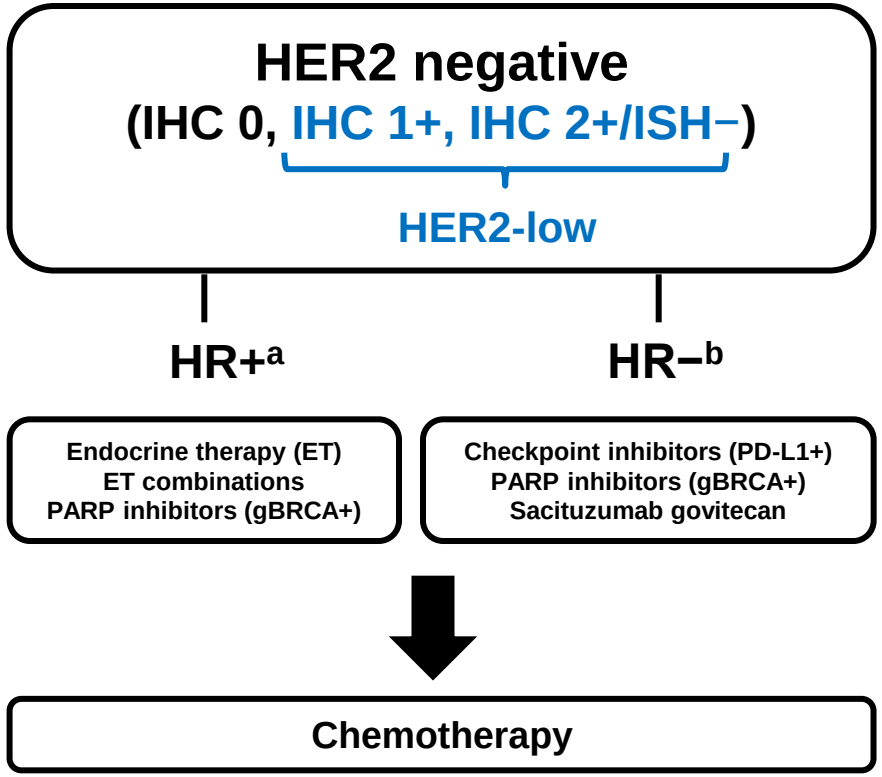


- Most HER2-low BC expressed hormone receptors:
  - **~65%-85% HR+ HER2-low**
  - **~35%-15% HR- HER2-low**

Modified from Tarantino P et al., J Clin Oncol 2020

HER2-low MBC: Unmet clinical need

Standard of Care Prior to DESTINY-Breast04



Similar prognosis between HER2 low and HER2 0

- No prognostic role for HER2 low expression

Historically, HER2-low mBC was treated as HER2− mBC, with limited options for later lines of therapy

- Therapeutic options for patients with HR+/HER2− mBC after CDK4/6i progression have limited efficacy

Limited benefit exists for patients who progress after multiple lines of chemotherapy

–In a pooled analysis of patients with HER2− mBC, eribulin and capecitabine provide minimal benefit, with a mPFS of ~4 months and mOS of ~15 months

Prior HER2 targeted therapies were not effective for patients with tumors that express lower levels of HER2

Negative Results of Monoclonal Abs & *'Old'* ADC in HER2-low BC

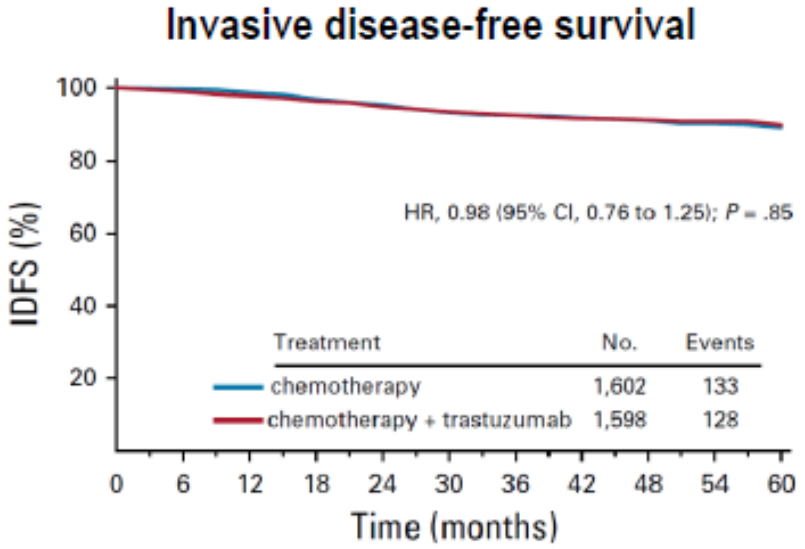
NSABP B-47 Trial: Adjuvant Trastuzumab in HER2 low BC

STRATIFICATION
- HER2 IHC Score (1+, 2+)
- Number of positive nodes (0–3, 4–9, 10+)
- Oestrogen receptor/progesterone receptor status
- Intended chemotherapy regimen (AC → WP, TC)

RANDOMISATION

GROUP 1
Chemotherapy*

GROUP 2
Chemotherapy* + Traztuzumab x 1 year



- In 2008, the centralized re-analysis of the NSABP B-31 trial identified 10% of HER2 non-amplified samples. These patients seemed to benefit from adjuvant trastuzumab.
- However, the NSABP B-47 showed absence of efficacy of adjuvant Trastuzumab in HER2 low BC.
- Similar negative results with Pertuzumab and T-DM1 in the advanced setting.

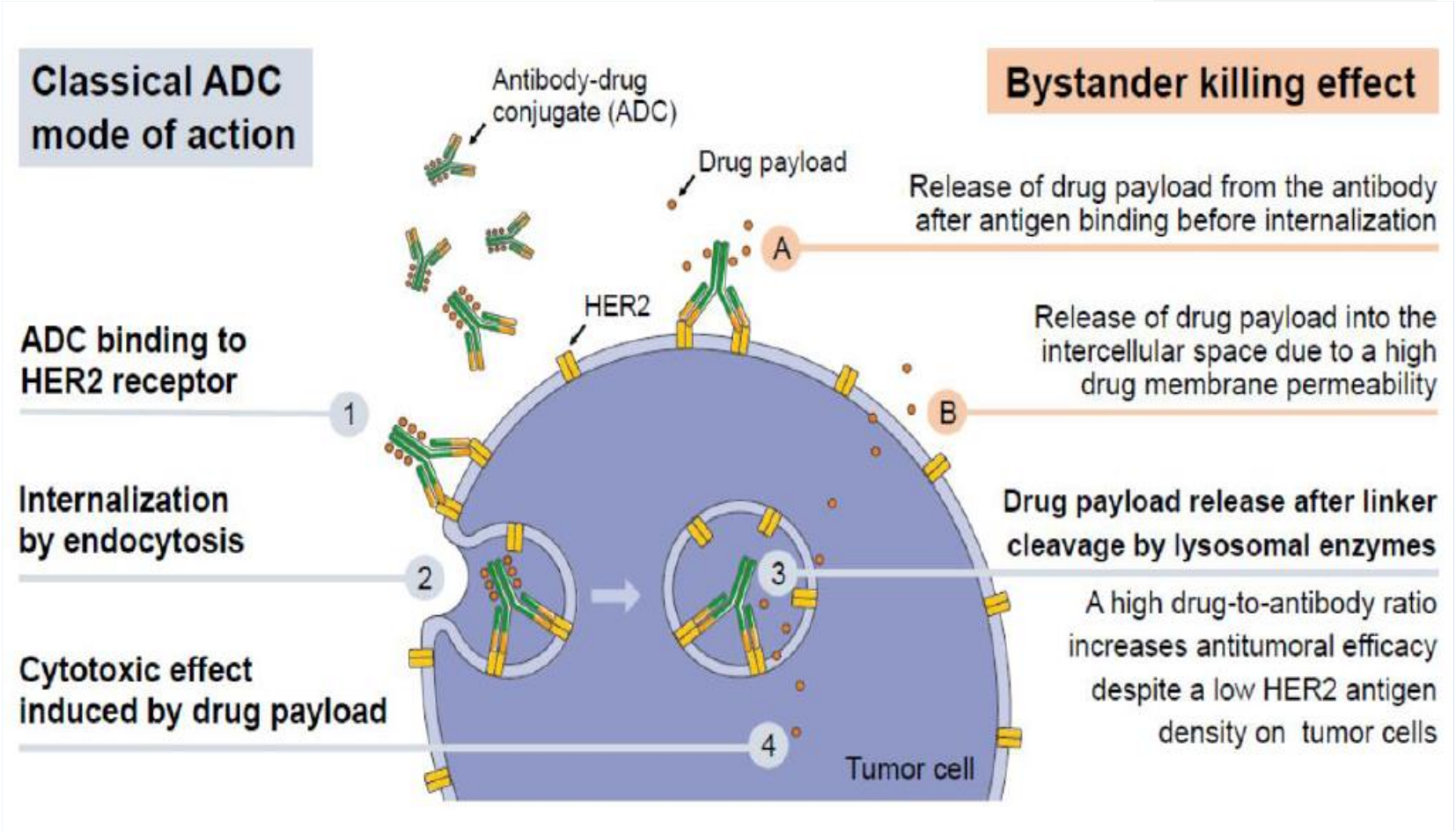
Paik S et al., NEJM 2008; Fehrenbacher L et al., JCO 2020; Gianni L et al., JCO 2010; Burris H etal., JCO 2011

The '*New*' ADCs

Antibody-Drug Conjugates (ADCs): Mechanism of Action

'*Old*' ADC

'*New*' ADC

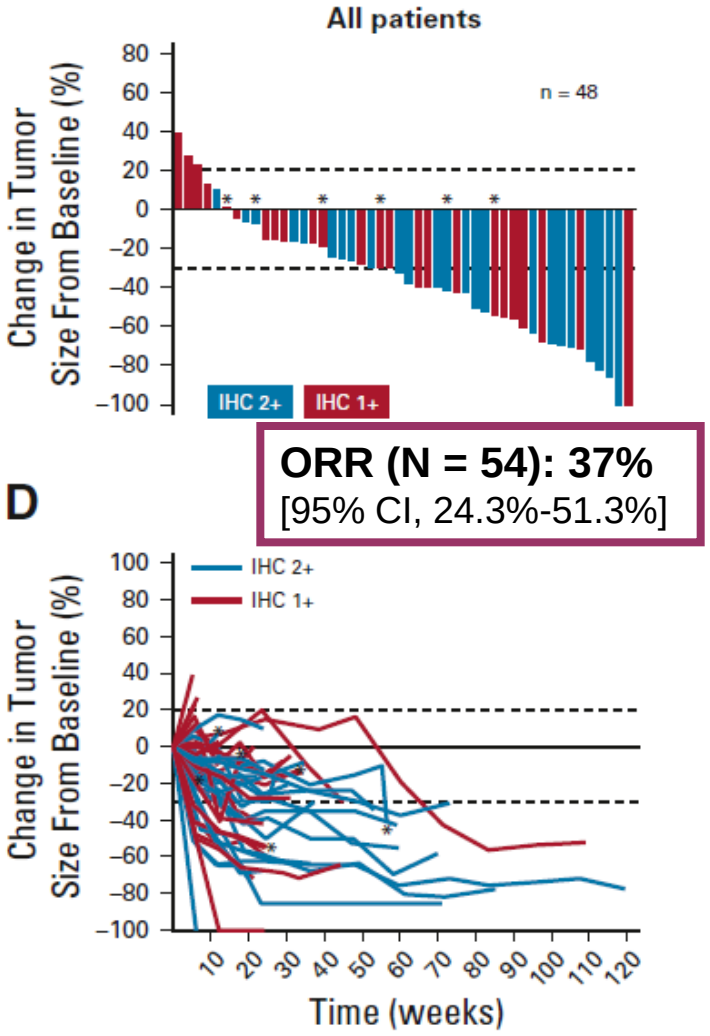


Rinnertalet G et al, Int J Mol Sci 2019

T-DXd in Heavily Pretreated HER2-low MBC

- Dose escalation and expansion phase I study.
- Population: advanced HER2 expressing/mutated solid tumors.
- HER2-low BC in cohorts 2c and 2e and treated with ≥ 1 dose of T-DXd at 5.4 (n = 21) or 6.4 mg/kg (n = 33).
- Median PFS: 11.1 mo

Characteristic	HER2-Low Breast Cancer N = 54
Median age (range), years	56.6 (33-75)
Country	
Japan	27 (50.0)
United States	27 (50.0)
ECOG performance status	
0	36 (66.7)
1	18 (33.3)
Median time from initial diagnosis (range), months[a]	105.0 (13.0-290.3)
Median No. of prior cancer regimens (range)	7.5 (2-16)
≥ 5 prior cancer regimens	45 (83.3)
CDK4/6 inhibitor	16 (29.6)
HER2-targeted therapy	10 (18.5)
Trastuzumab	10 (18.5)
Pertuzumab	7 (13.0)
T-DM1	5 (9.3)
Other	1 (1.9)
Previous cancer surgery	48 (88.9)



ORR (N = 54): 37%
[95% CI, 24.3%-51.3%]

Modi S et al., J Clin Oncol 2020

DESTINY-Breast04: Phase III Study of T-Dxd in HER2-low MDC

An open-label, multicenter study (NCT03734029)

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

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−

Key Eligibility Criteria
- HER2-low (IHC 1+ or IHC 2+/ISH-) unresectable and/or MBC
- ≥1 prior line(s) of chemo in the metastatic setting or disease recurrence ≤6 months after adjuvant therapy
- ≥1 line(s) of endocrine therapy if HR+ MBC

Chemotherapy, n (%)	
Eribulin	94 (51.1)
Capecitabine	37 (20.1)
Nab-paclitaxel	19 (10.3)
Gemcitabine	19 (10.3)
Paclitaxel	15 (8.2)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

Hierarchical testing

PFS in HR+
↓
PFS in all patients
↓
OS in HR+
↓
OS in all patients

Modi S et al., ASCO 2022 & NEJM 2022

DESTINY-Breast04: Baseline Characteristics

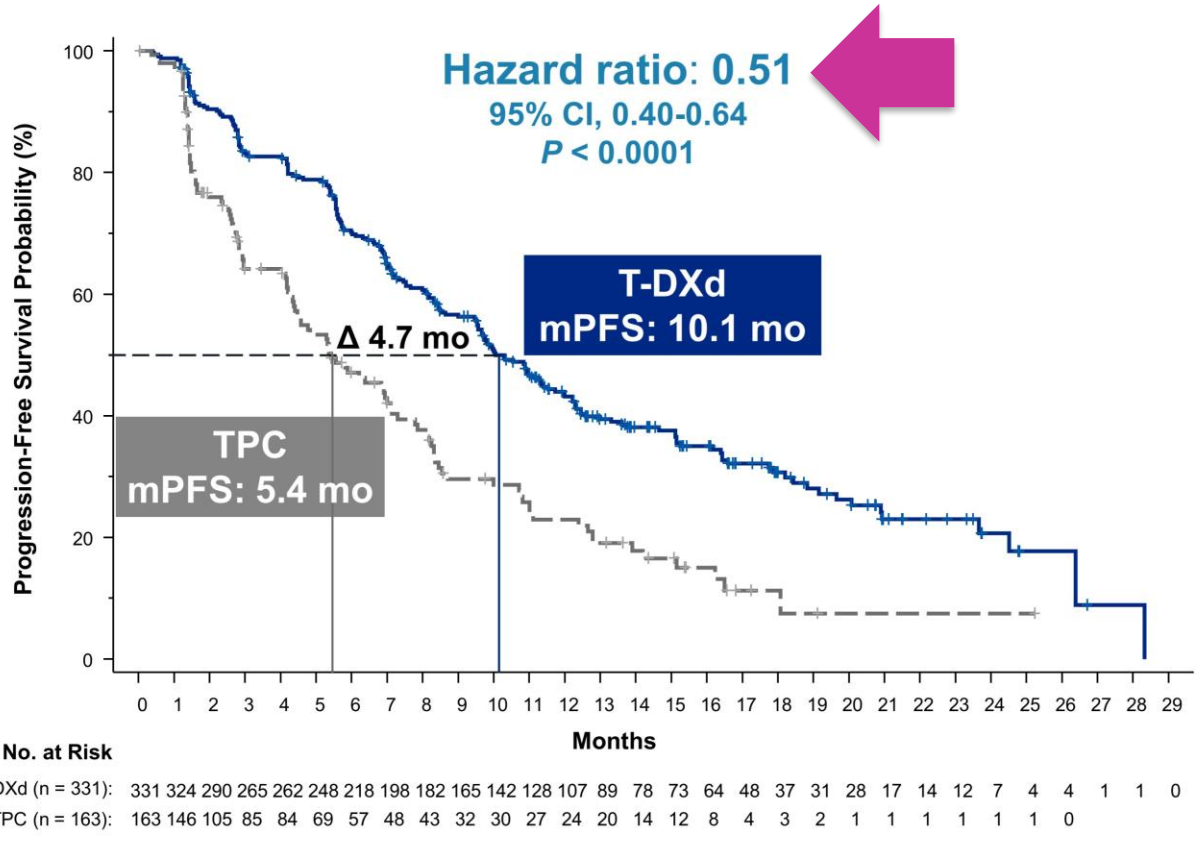
	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy (metastatic setting)				
Number of lines, median (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Number of lines, median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Number of lines, median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)
Brain metastases at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)

Modi S et al., ASCO 2022 & NEJM 2022

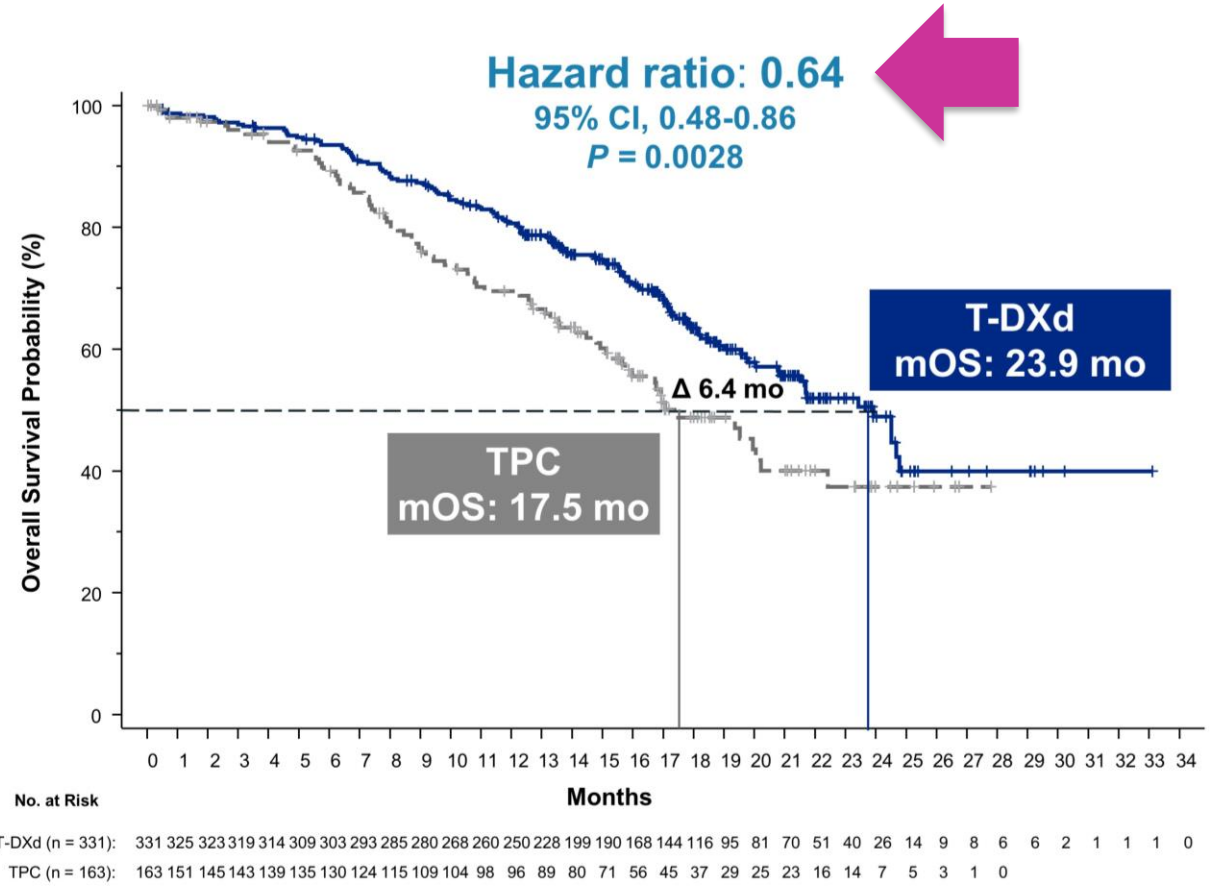
DESTINY-Breast04: PFS (Primary End-point) & OS (HR+)

median follow-up was 18.4 months

Hormone receptor–positive



Hormone receptor–positive

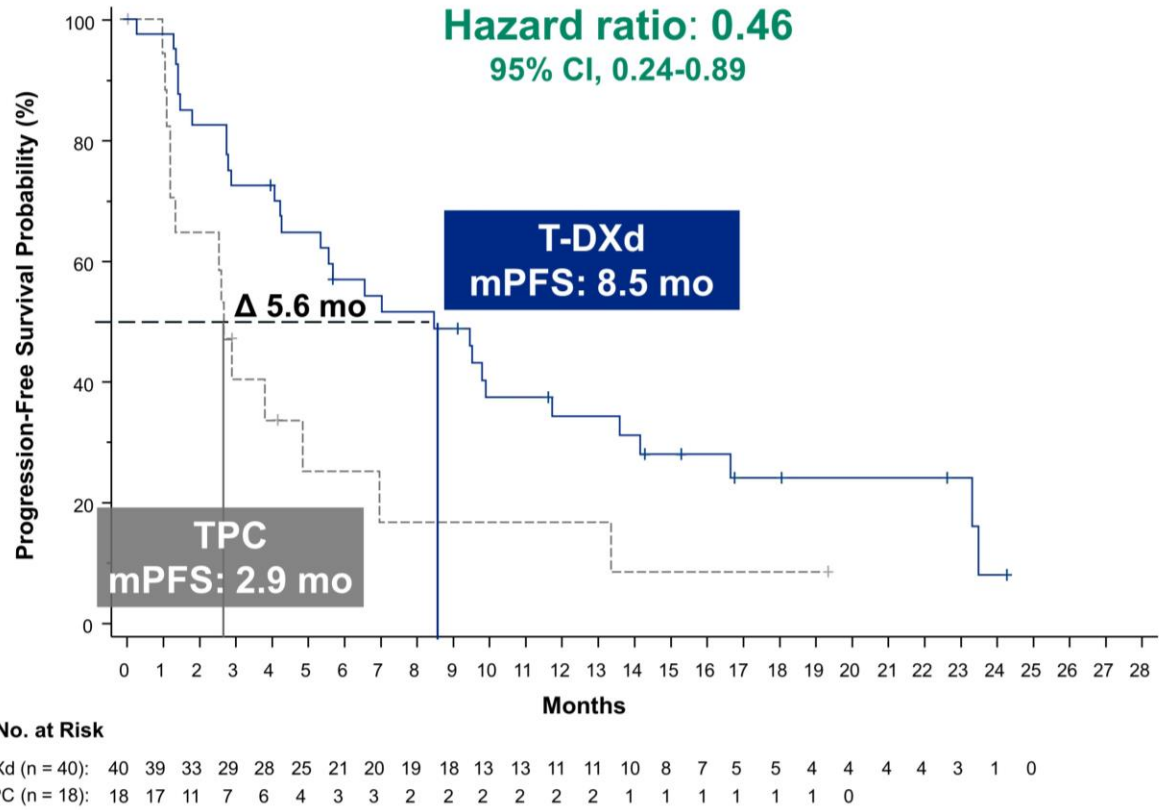


Benefit was observed across all stratification subgroups, including according to HER2-low (IHC 1+ or IHC 2+/ISH-) and prior CDK4/6i

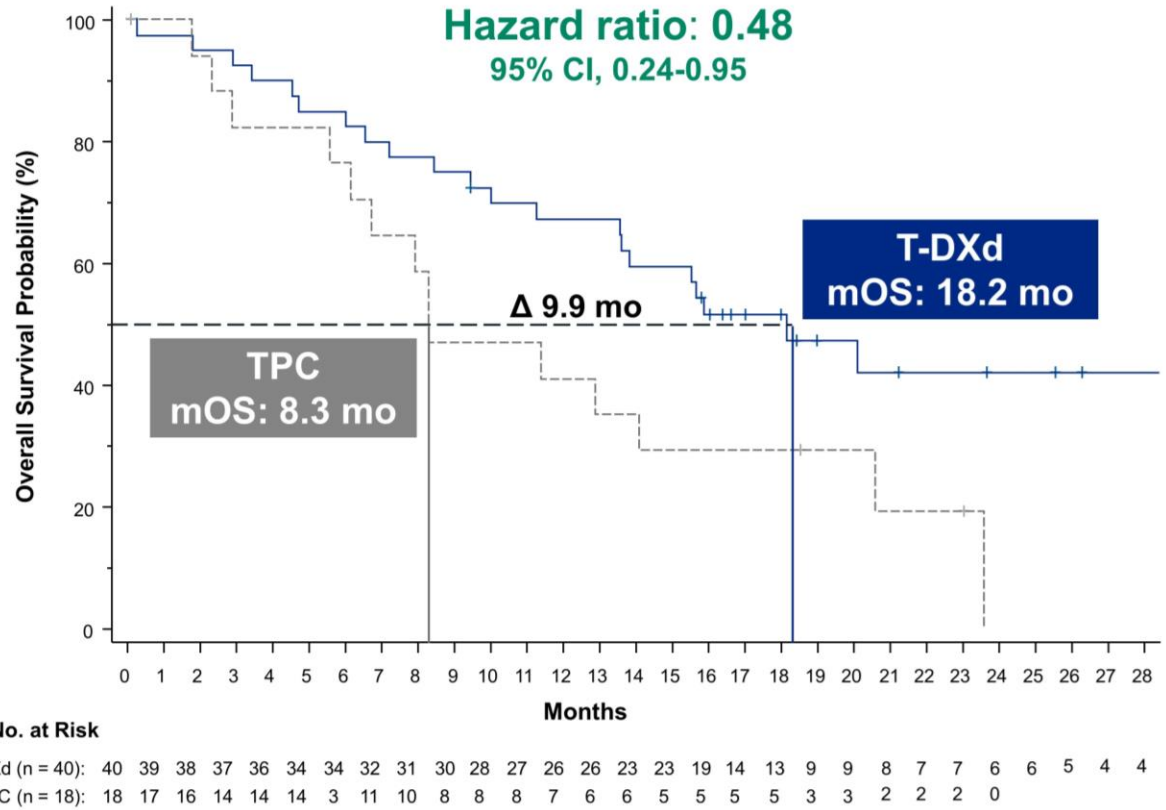
Modi S et al., ASCO 2002 & NEJM 2022

DESTINY-Breast04: PFS & OS in HR- (Exploratory analysis)

PFS



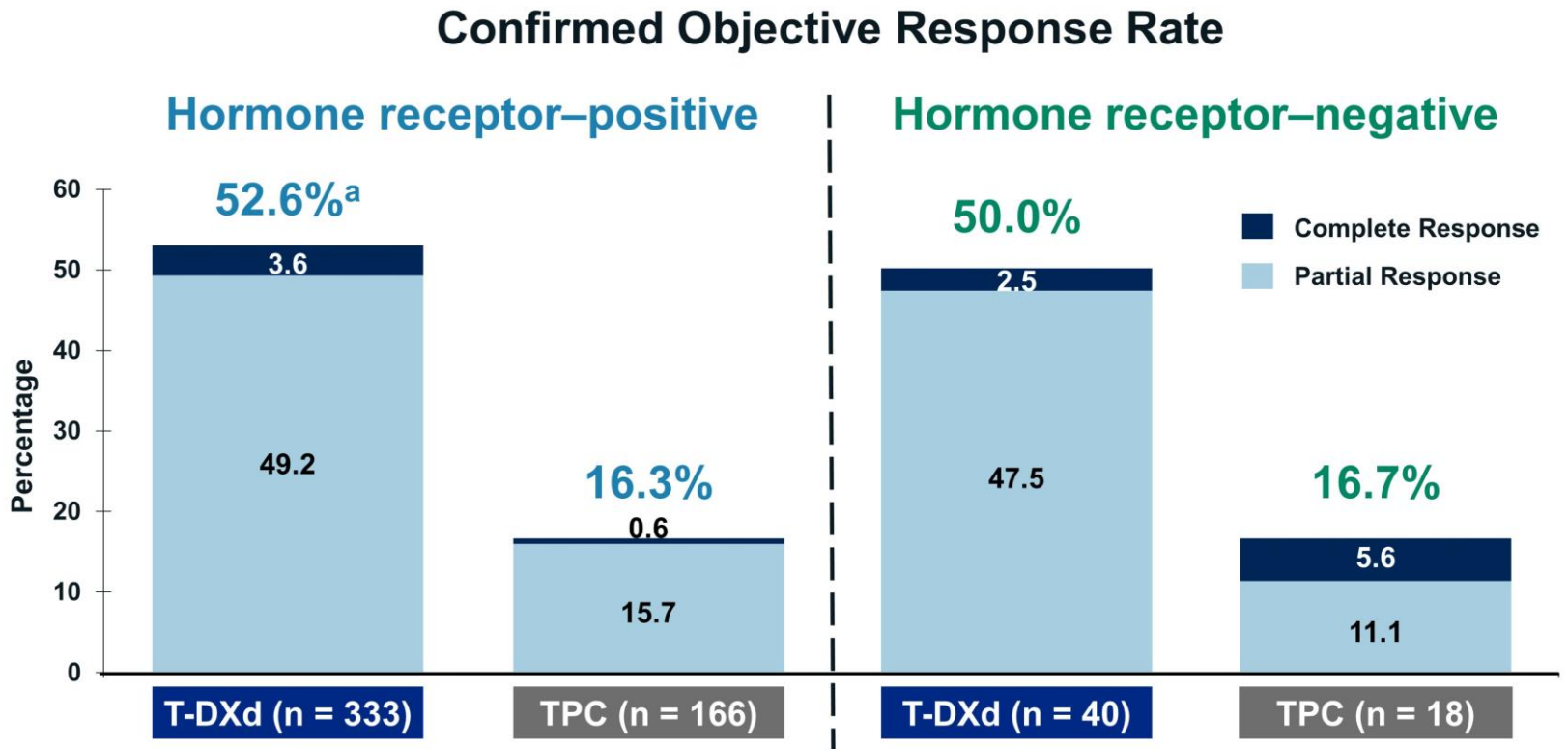
OS



HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based on data from the electronic data capture corrected for misstratification.

Modi S et al., ASCO 2022 & NEJM 2022

DESTINY-Breast04: ORR

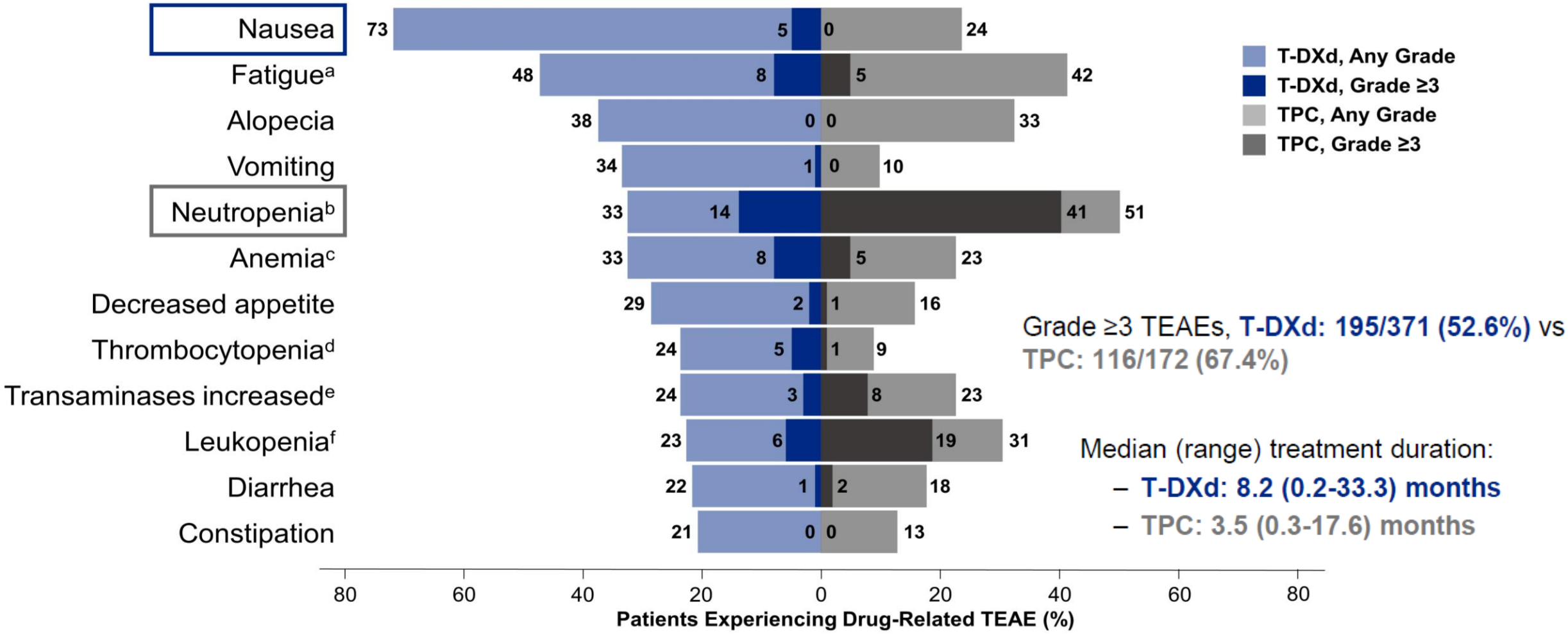


	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded independent central review.

Modi S et al., ASCO 2022 & NEJM 2022

DESTINY-Breast04: Safety



Grade ≥3 TEAEs, **T-DXd: 195/371 (52.6%)** vs TPC: 116/172 (67.4%)

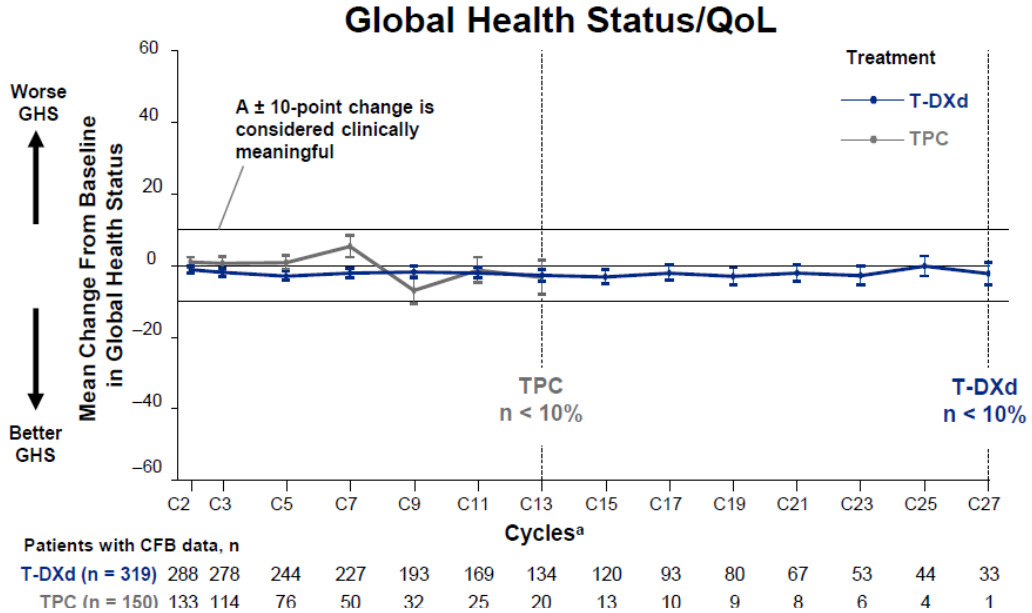
Median (range) treatment duration:
- **T-DXd: 8.2 (0.2-33.3) months**
- TPC: 3.5 (0.3-17.6) months

Adjudicated as drug-related ILD/pneumonitis[a]

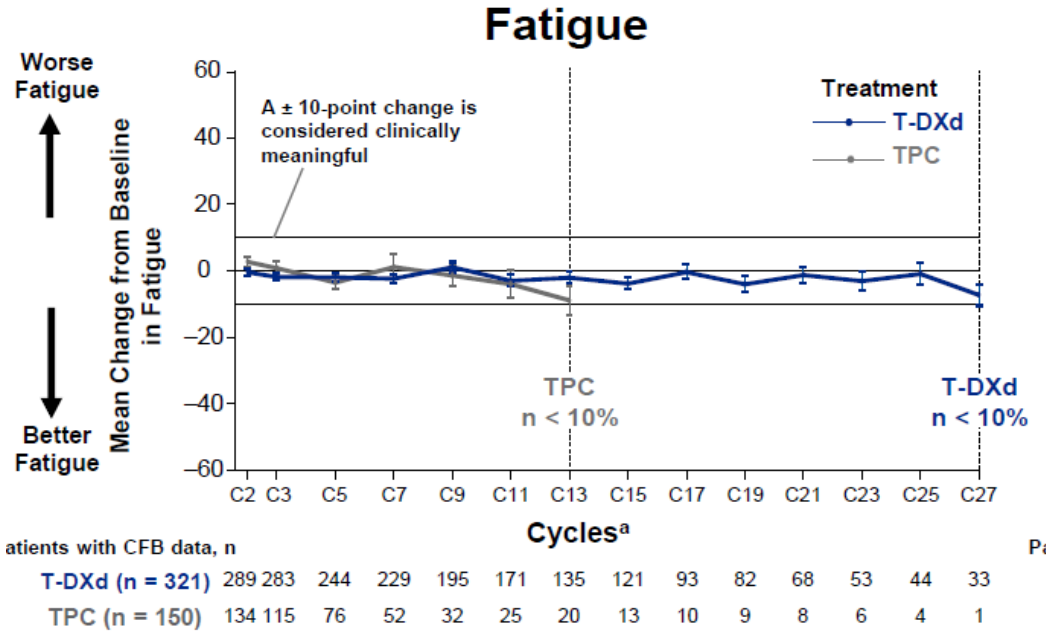
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

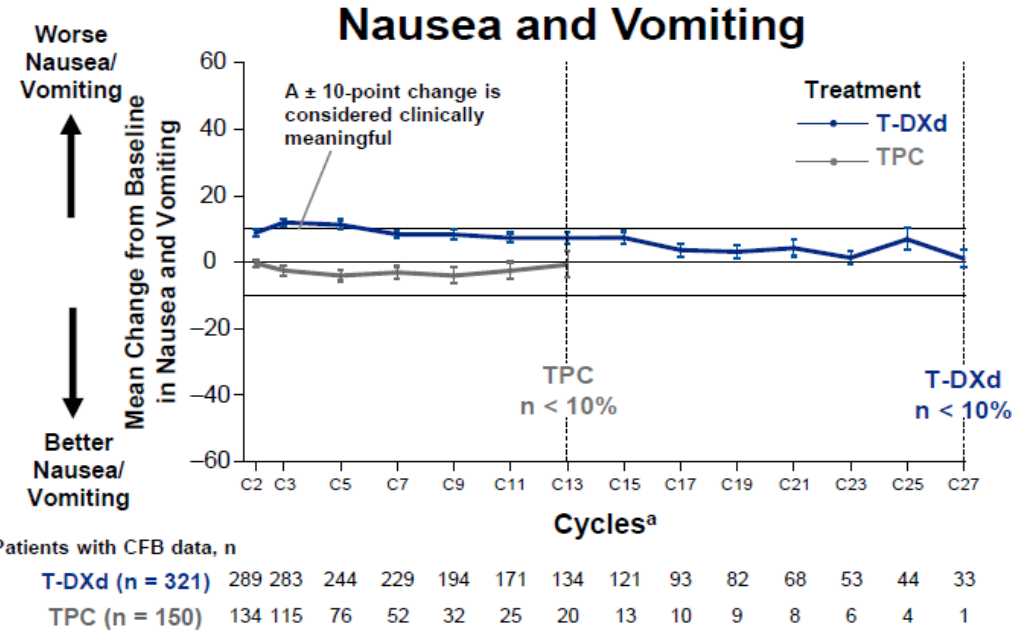
Modi S et al., ASCO 2022 & NEJM 2022

DESTINY-Breast04: Quality of Life



- GHS/QoL was maintainted with T-Dxd and TPC (QLQ-C30).
- Fatigue scores remained stable over time in both treatment arms.
- **With T-DXd, an increase in nausea and vomiting scores was only clinically relevant in early cycles,** after which scores decreased and remained stable over time.

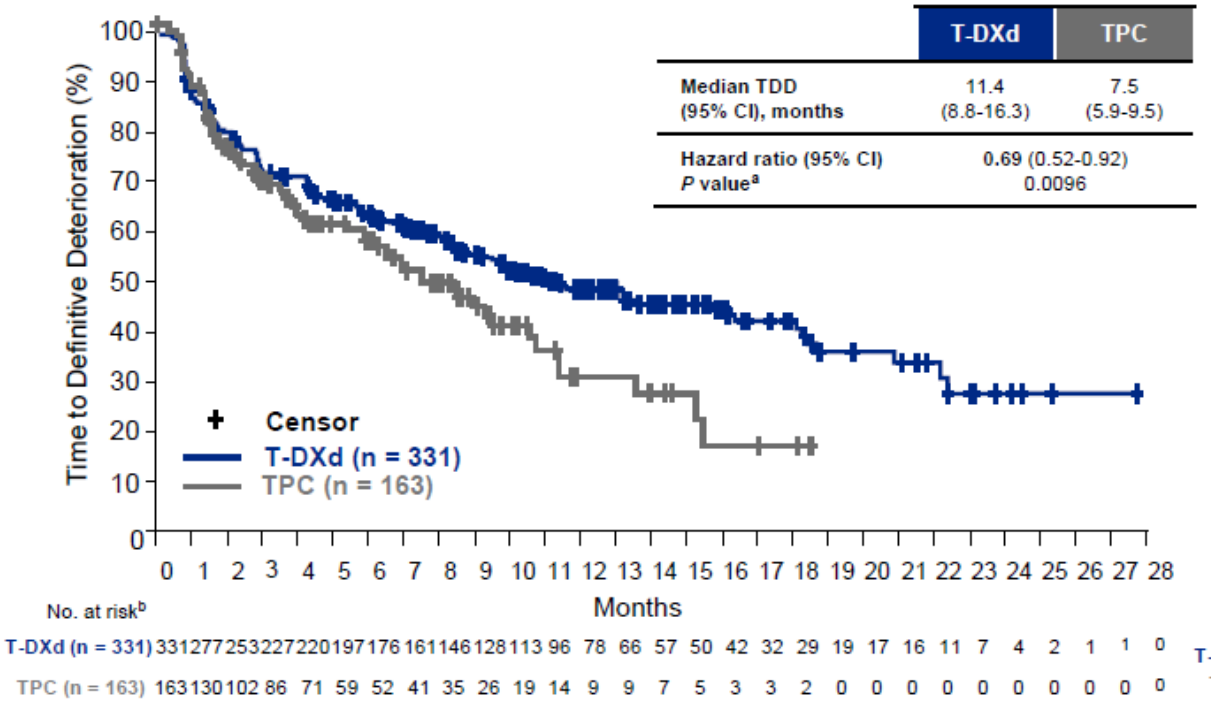




Naoto T. Ueno et al., ESMO 2022

DESTINY-Breast04: Quality of Life

GHS/QoL

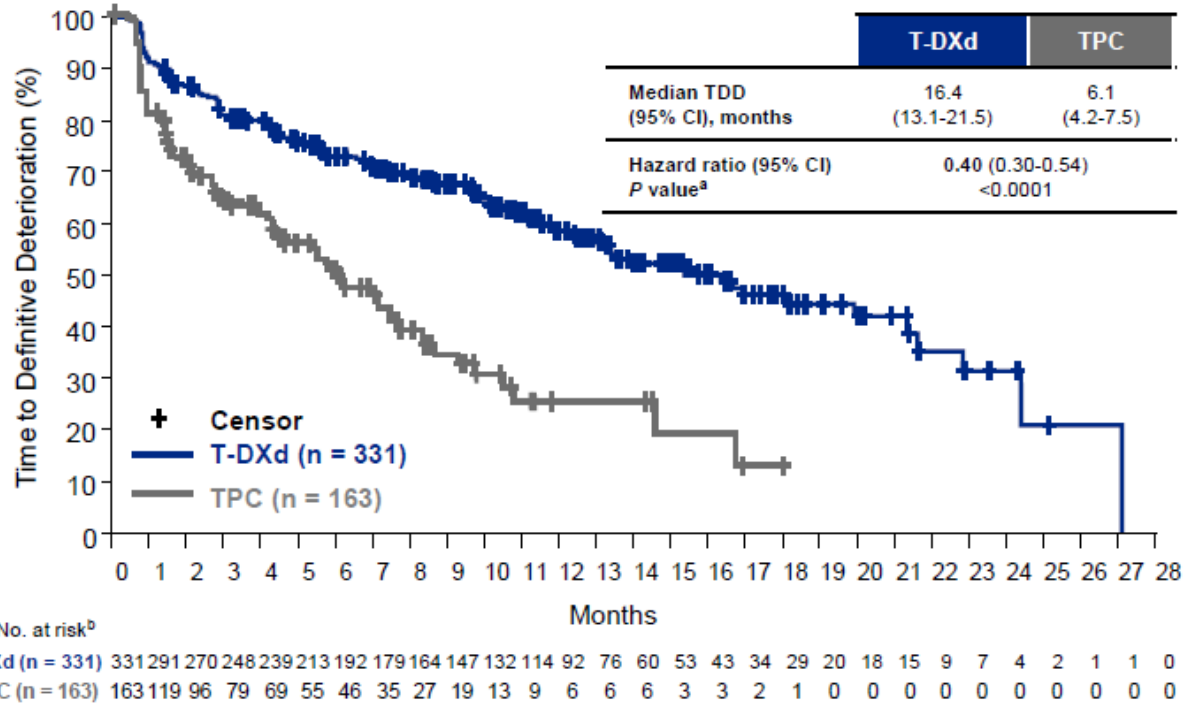


	T-DXd	TPC
Median TDD (95% CI), months	11.4 (8.8-16.3)	7.5 (5.9-9.5)
Hazard ratio (95% CI)	0.69 (0.52-0.92)	
P value[a]	0.0096	

No. at risk[b]

T-DXd (n = 331)	331	277	253	227	220	197	176	161	146	128	113	96	78	66	57	50	42	32	29	19	17	16	11	7	4	2	1	1	0
TPC (n = 163)	163	130	102	86	71	59	52	41	35	26	19	14	9	9	7	5	3	3	2	0	0	0	0	0	0	0	0	0	0

Pain Symptoms



	T-DXd	TPC
Median TDD (95% CI), months	16.4 (13.1-21.5)	6.1 (4.2-7.5)
Hazard ratio (95% CI)	0.40 (0.30-0.54)	
P value[a]	<0.0001	

No. at risk[b]

T-DXd (n = 331)	331	291	270	248	239	213	192	179	164	147	132	114	92	76	60	53	43	34	29	20	18	15	9	7	4	2	1	1	0
TPC (n = 163)	163	119	96	79	69	55	46	35	27	19	13	9	6	6	6	3	3	2	1	0	0	0	0	0	0	0	0	0	0

- **Time to definitive deterioration of GHS/QoL and pain was longer among patients who received T-DXd vs TPC (QLQ-C30)**
- T-DXd treatment delays the deterioration of GHS/QoL and shows a QoL benefit of T-DXd vs TPC in patients with HR+/HER2-low mBC

Naoto T. Ueno et al., ESMO 2022

T-Dxd in HER2-low BC Approval

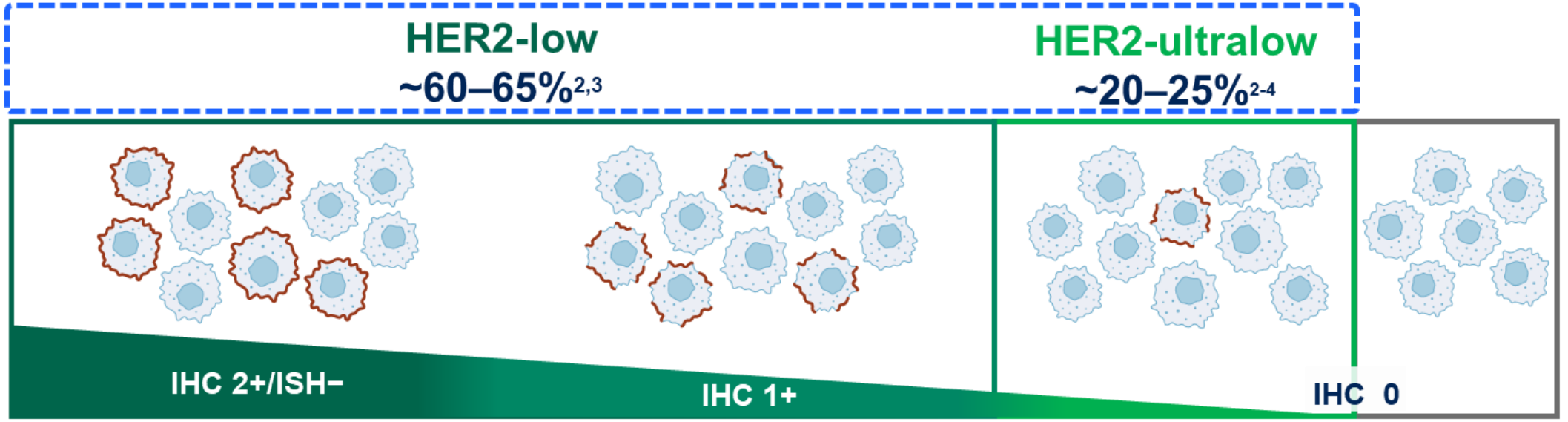
- On **August 2022**, **FDA** approved T-Dxd for adult patients with unresectable or metastatic HER2-low breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.

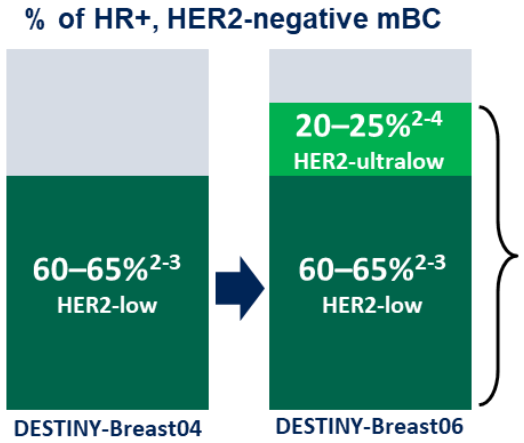
- On **January 2023**, the **EMA** Commission approved T-DXd with the same indication of the FDA.

- A **Dicembre 2023**, l'**AIFA** ha approvato T-Dxd in monoterapia per il trattamento di pazienti adulti con cancro della mammella HER2-low non resecabile o metastatico, che hanno ricevuto precedente chemioterapia per malattia metastatica o che hanno sviluppato recidiva della malattia durante o entro 6 mesi dal completamento della chemioterapia adiuvante

HER2-low & HER2-ultralow BC Definition

Majority of HR+, HER2- MBC express low levels of HER2





In DESTINY-Breast06 trial, T-DXd's efficacy is studied in HR+, HER2-low and HER2-ultralow, CT-naïve mBC patients when compared against physician's choice single agent chemotherapy

DESTINY-Breast06: Phase III Study of T-Dxd in HER2-low/ultralow MBC

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)

*History of HER2-low (IHC 1+ or IHC 2+/ISH−) or negative expression (IHC 0) by local test.
HER2-low or HER2-ultralow (IHC 0 with membrane staining) expression as determined by the central laboratory result established on a tissue sample taken in the metastatic setting

R 1:1

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

TPC
(n=430)

HER2-low = 713
HER2-ultralow = 153†

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

ENDPOINTS

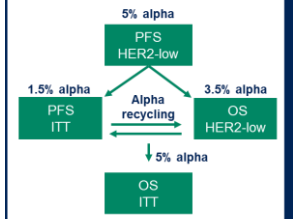
Primary

- PFS (BICR) in HER2-low

Key secondary

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

Multiple testing procedure*



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‡

Curigliano G. et al., ASCO 2024; Bardia A. et al., NEJM 2024

DESTINY-Breast06: 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)
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)
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)

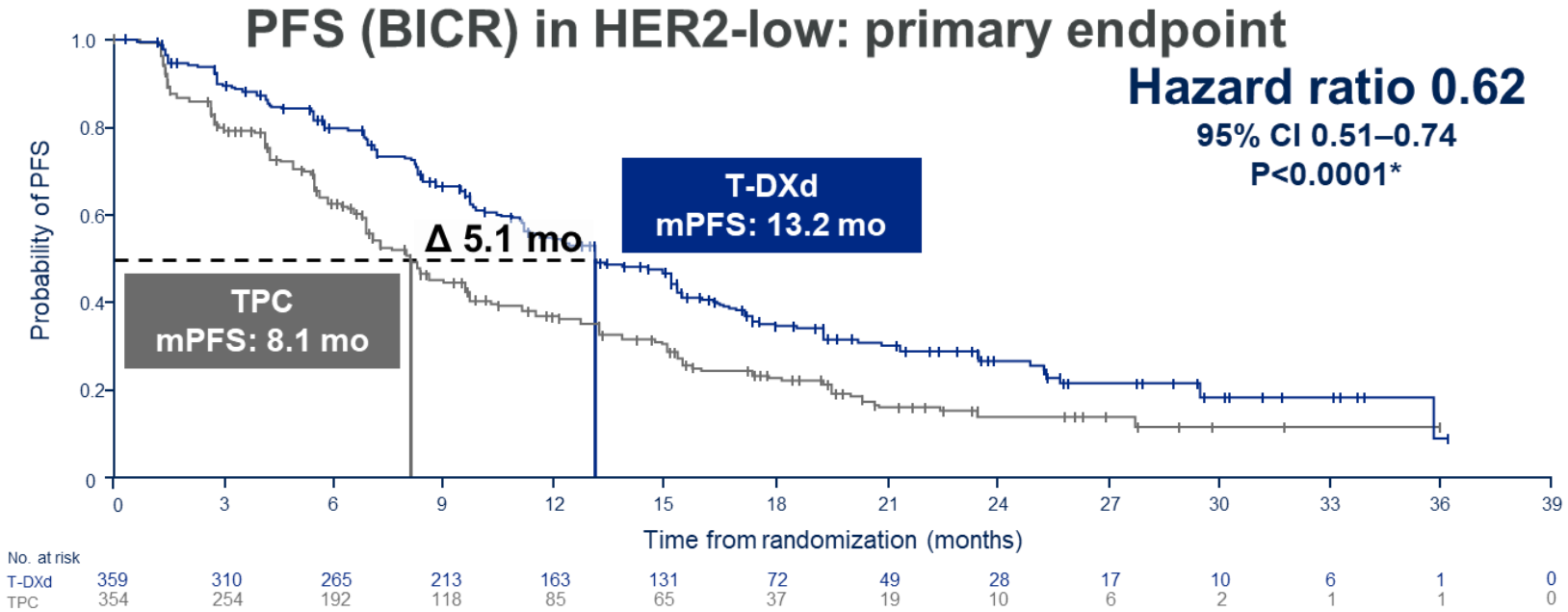
Curigliano G. et al., ASCO 2024; Bardia A. et al., NEJM 2024

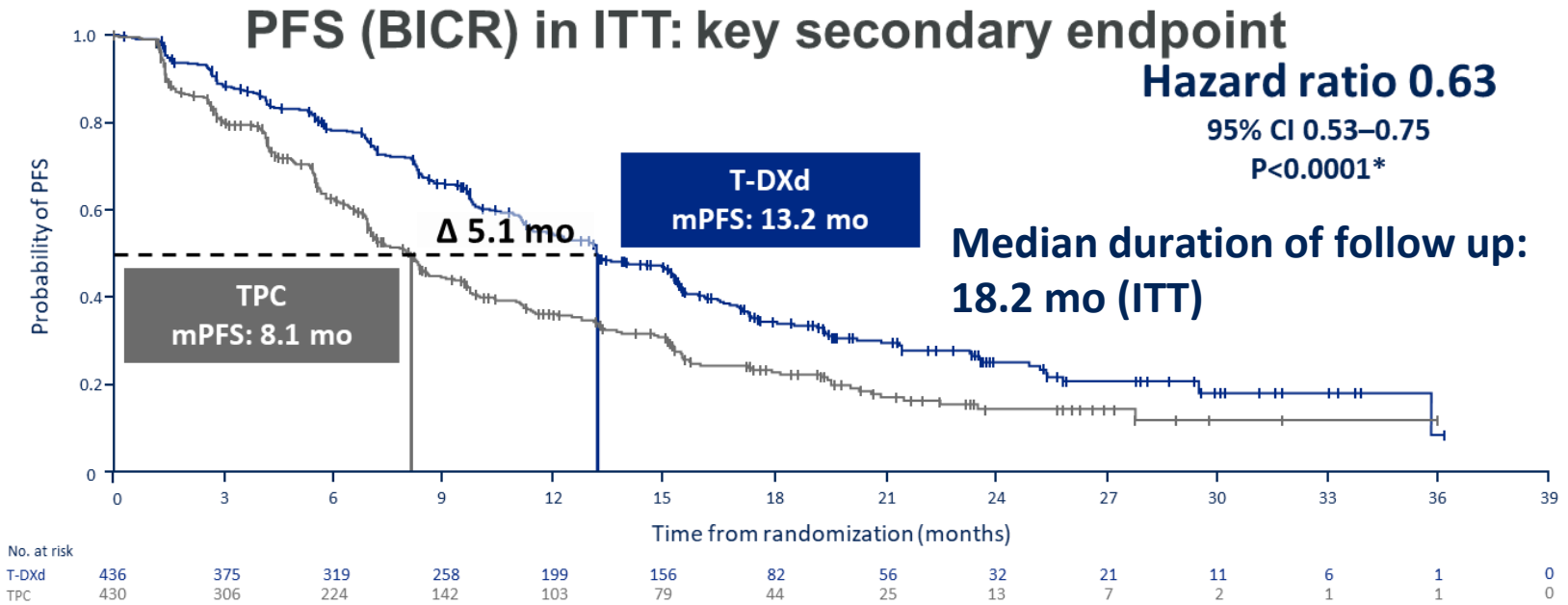
Results from central scoring

- Of samples scored as HER2-low locally, **94%** met DESTINY-Breast06 inclusion criteria (were either **HER2-low** or **HER2-ultralow** by central testing)
- **Overall percent agreement** was **77.8%** for HER2-low*
- Of samples scored as IHC 0 locally, central testing found
  - 35% were IHC 0 absent membrane staining
  - **40%** were **HER2-ultralow**
  - **24%** were **HER2-low**

Viale G et al (Destiny-06 Central Revision), ESMO 2024

DESTINY-Breast06: PFS

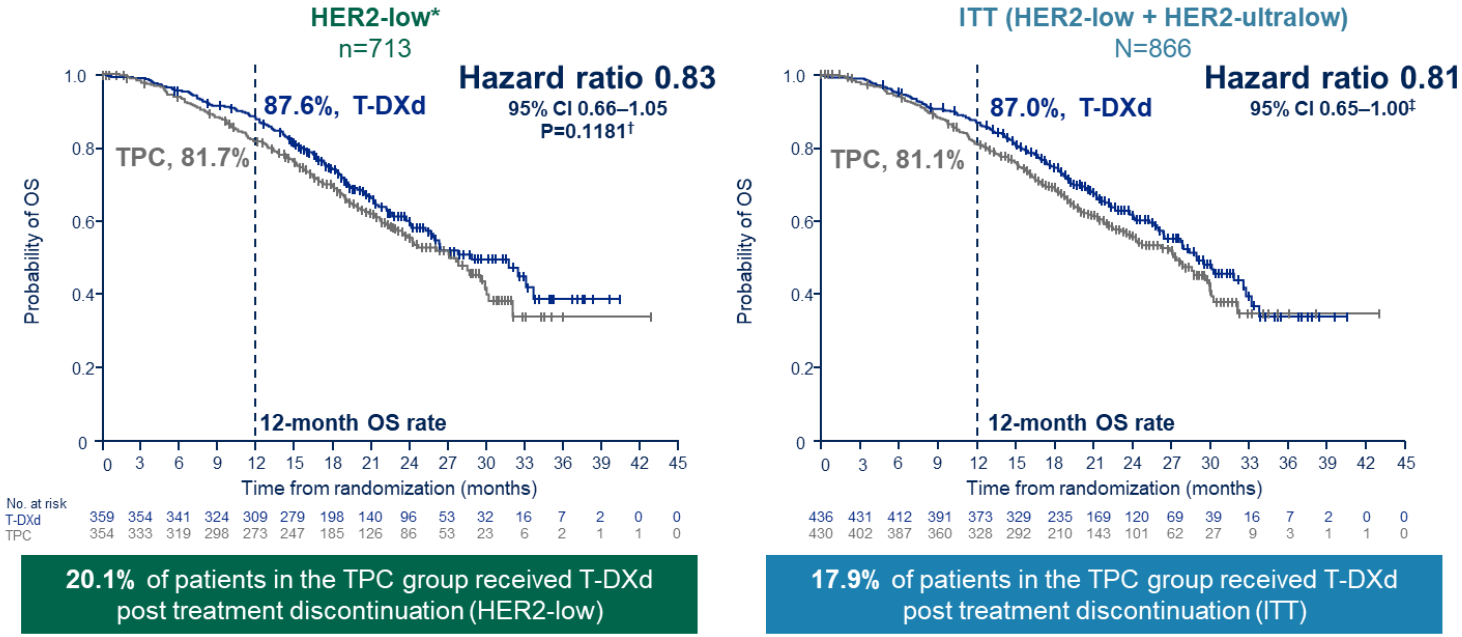




Curigliano G. et al., ASCO 2024; Bardia A. et al., NEJM 2024

DESTINY-Breast06: secondary/exploratory outcomes

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



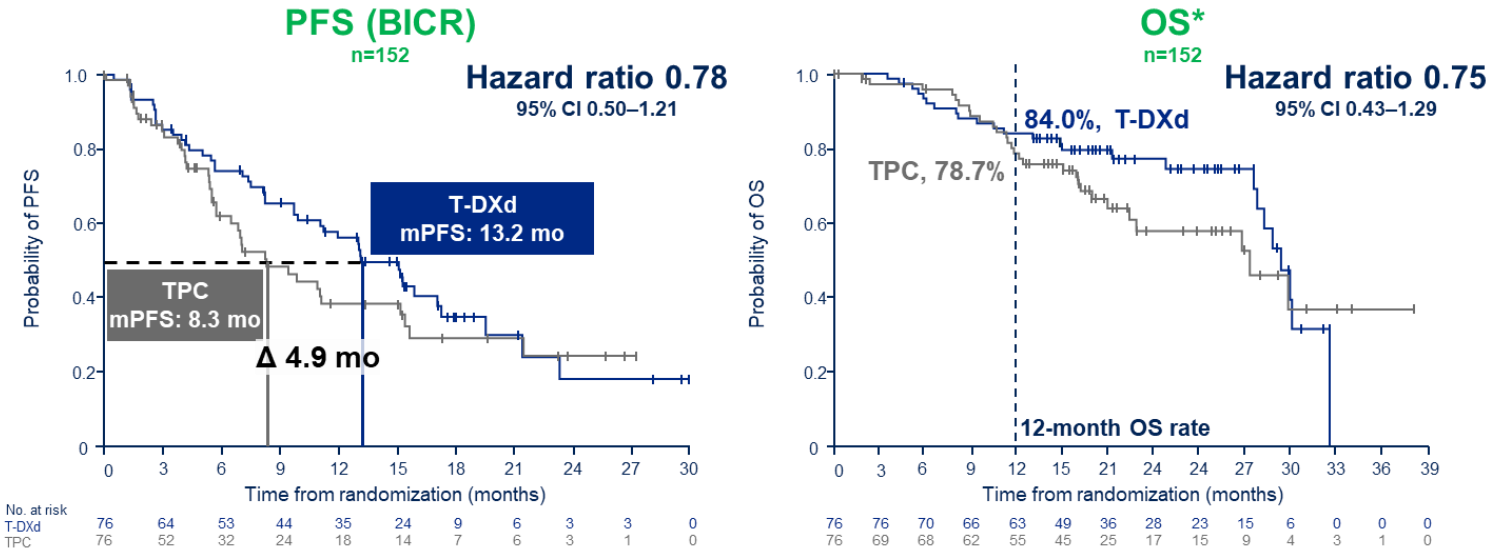
20.1% of patients in the TPC group received T-DXd post treatment discontinuation (HER2-low)

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

Confirmed ORR, n (%)

HER2-low*		ITT	
T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)
203 (56.5)	114 (32.2)	250 (57.3)	134 (31.2)

PFS and OS in HER2-ultralow: prespecified exploratory analyses



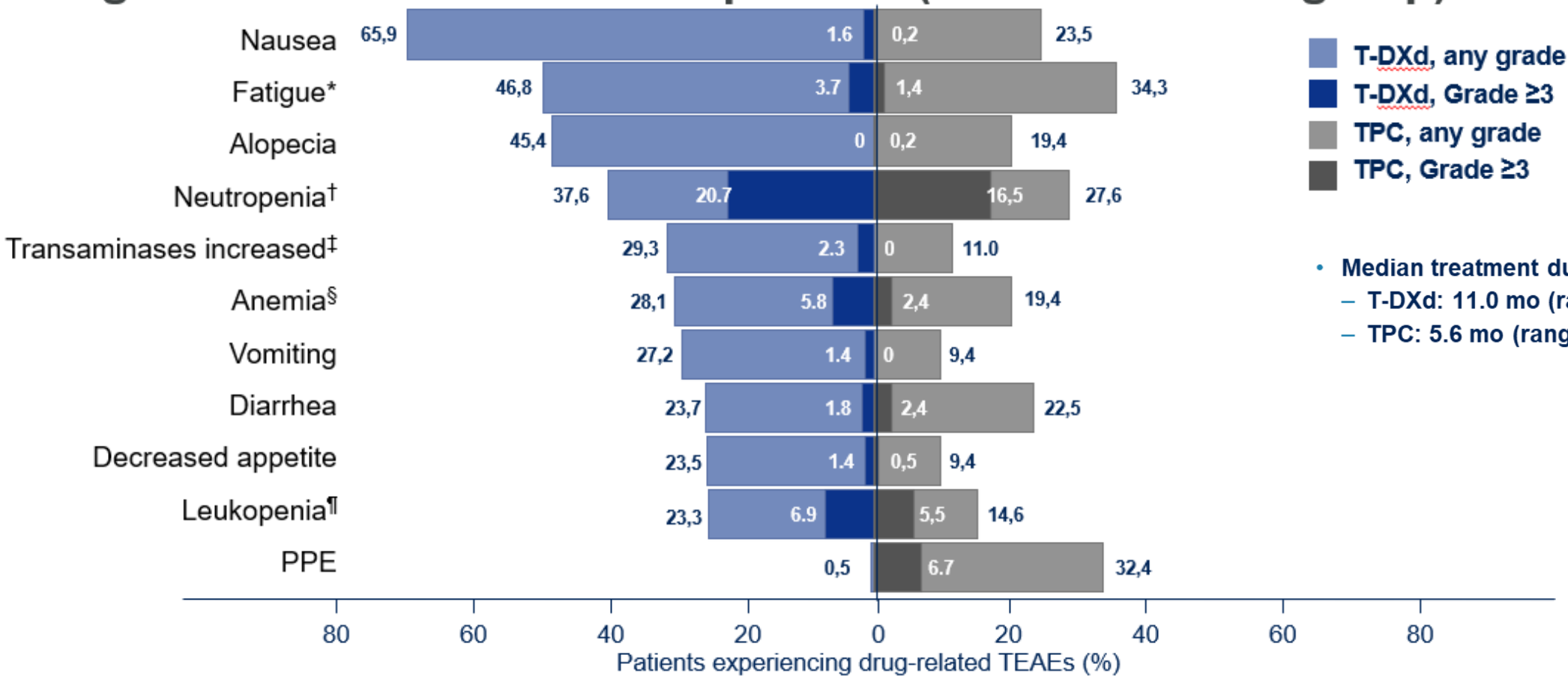
Confirmed ORR, n (%)

HER2-ultralow*	
T-DXd (n=76)	TPC (n=76)
47 (61.8)	20 (26.3)

Curigliano G. et al., ASCO 2024;
Bardia A. et al., NEJM 2024

DESTINY-Breast06: Safety

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



- Median treatment duration:
  - T-DXd: 11.0 mo (range 0.4–39.6)
  - TPC: 5.6 mo (range 0.1–35.9)

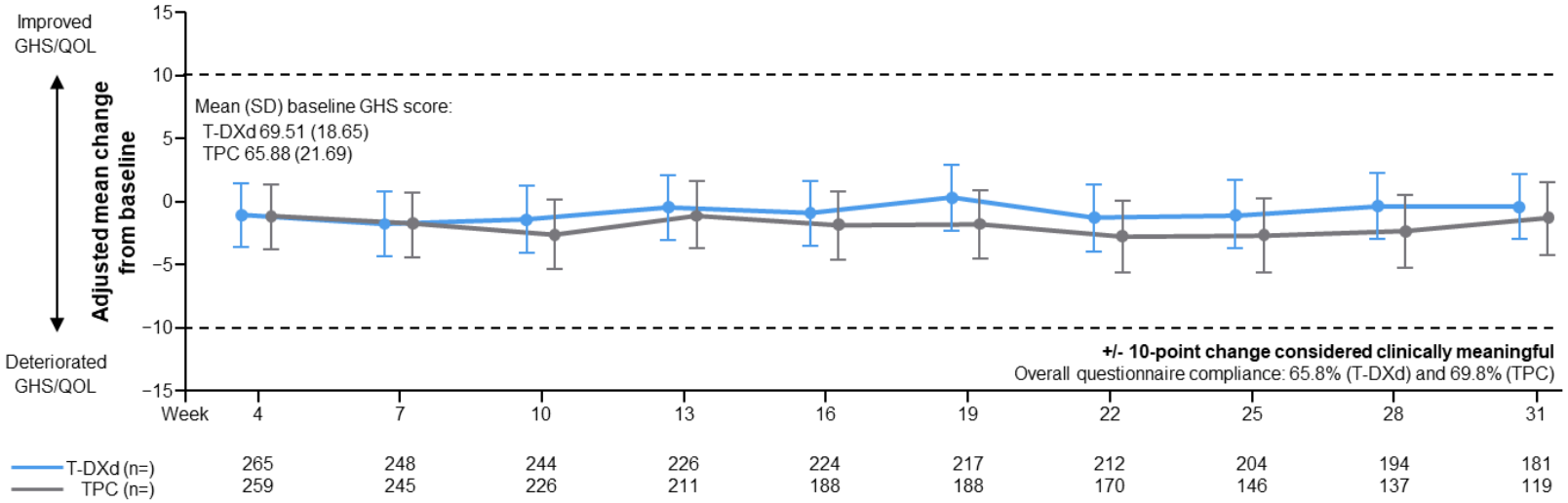
Adjudicated as drug-related interstitial lung disease / pneumonitis*

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)

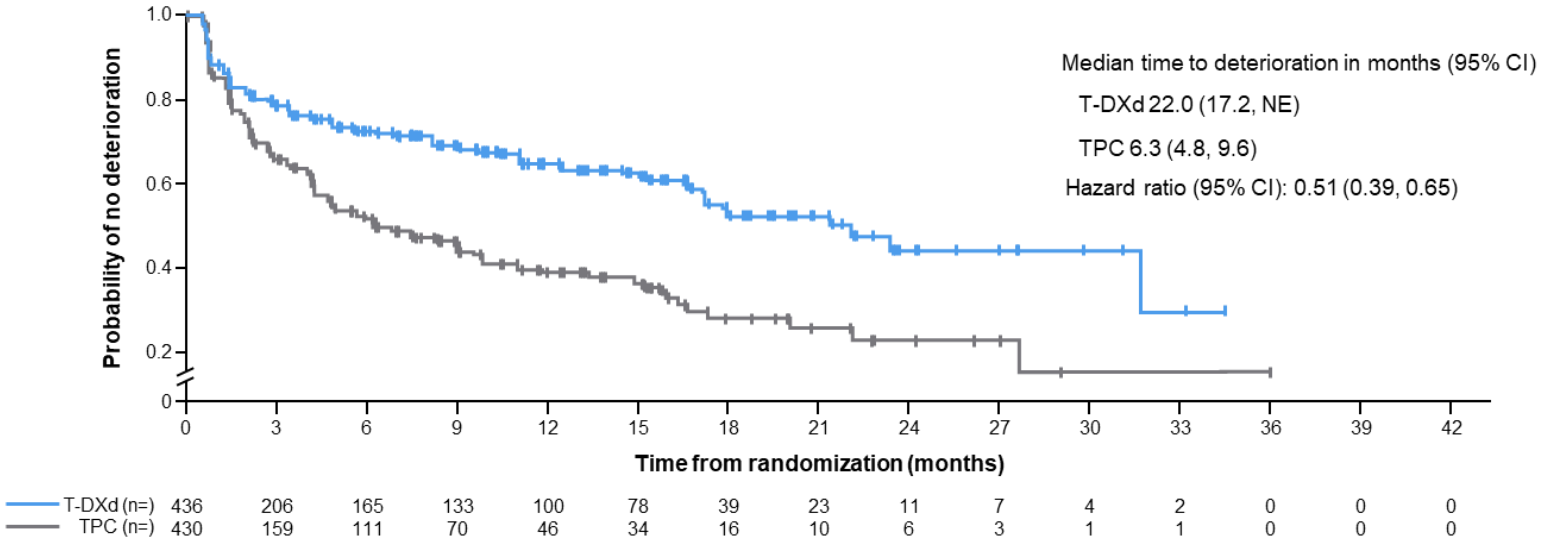
Curigliano G. et al., ASCO 2024; Bardia A. et al., NEJM 2024

DESTINY-Breast06: Quality of Life (QoL)

Mean change from baseline in QLQ-C30 GHS/QOL over 31 weeks or until PD (whichever earlier): ITT (HER2-low and HER2-ultralow)



Deterioration in QLQ-C30 pain: ITT

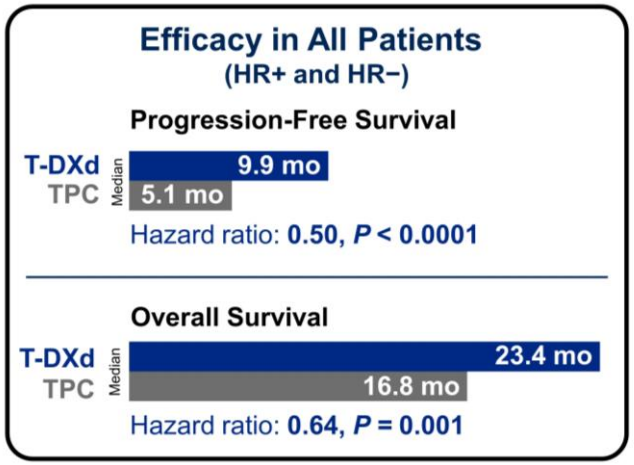


- Duration of treatment was approximately twice as long with T-DXd versus TPC.
- **Overall GHS/QOL was maintained during treatment with T-DXd .**
- **Time to deterioration was delayed in physical and role functioning, and pain, versus TPC.**

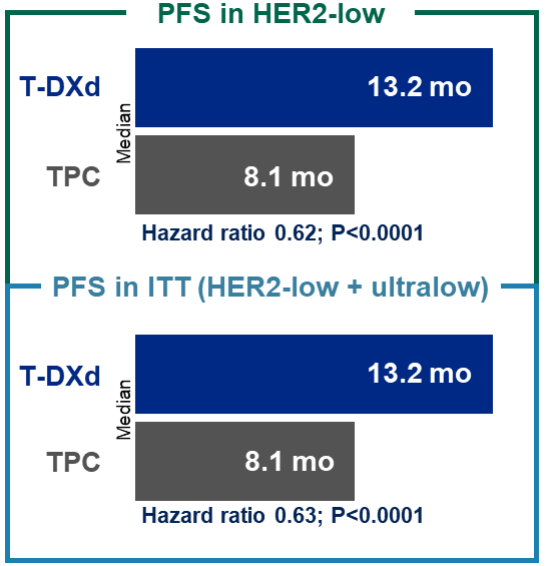
Hu X. et al., ESMO 2024

Conclusions (1)

- HER2-low BC emerges as a new druggable entity, through the delivery of payloads
- T-Dxd is the first HER2-targeted therapy to demonstrate efficacy in HER2-low BC
  - Similar magnitude of benefit across all subgroups
  - More data are needed in HER2-low/HR-
  - Peculiar toxicity of T-Dxd, management is crucial!



- Recently, 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 (an earlier line of treatment than DESTINY-Breast04)
  - Results in HER2-ultralow were consistent with HER2-low



Conclusions (2)

- **The FDA has granted priority review to T-Dxd for adults with metastatic HER2-low or HER2-ultralow BC previously treated with at least 1 type of endocrine therapy in the metastatic setting**

- It may be advisable for patients with HR+ MBC scored as HER2 IHC 0 to be reassessed to determine if they may be eligible for treatment with T-DXd.
  - HER2 status can change between early and relapsed setting.

- **Novel anti-HER2 agents are currently investigated in HER2-low BC (‘*New*’ ADC, Vaccines and Bispecific Antibodies)**

Grazie per l’attenzione