HER2-low Advanced and Metastatic Breast Cancer: How Low Can You Go?

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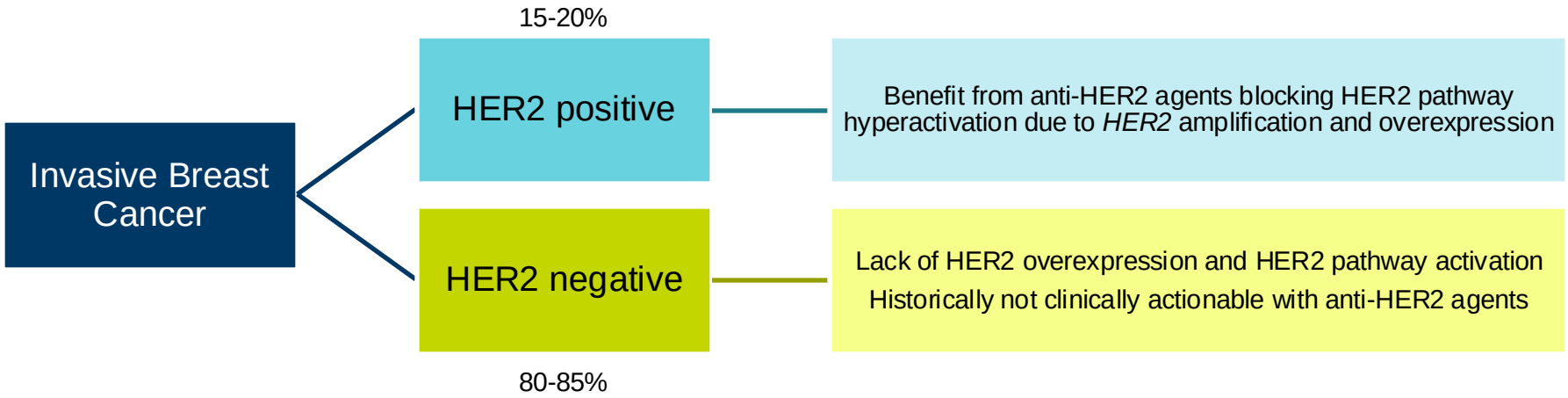
Historically 2 Different Treatment Algorithms for MBC Based on HER2 Receptor Status[1,2]

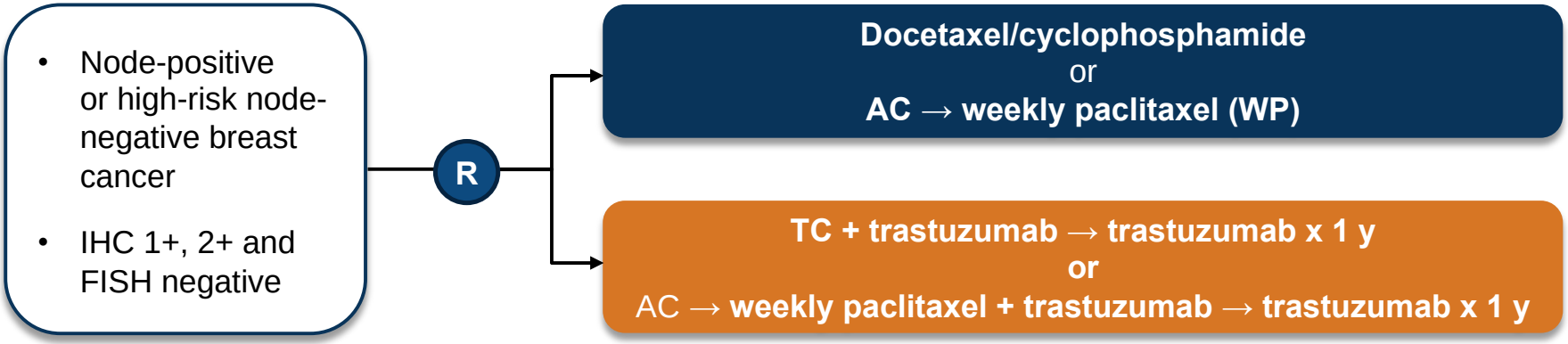


HER2 status in patients with breast cancer is routinely determined via IHC to evaluate HER2 protein expression levels, ISH to assess HER2 gene amplification, or combined interpretation of the IHC and ISH assays

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Invasive Breast Cancer V8. 2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed September 13, 2021. **2.** Marchiò C, et al. *Semin Cancer Biol*. 2021;72:123-135.

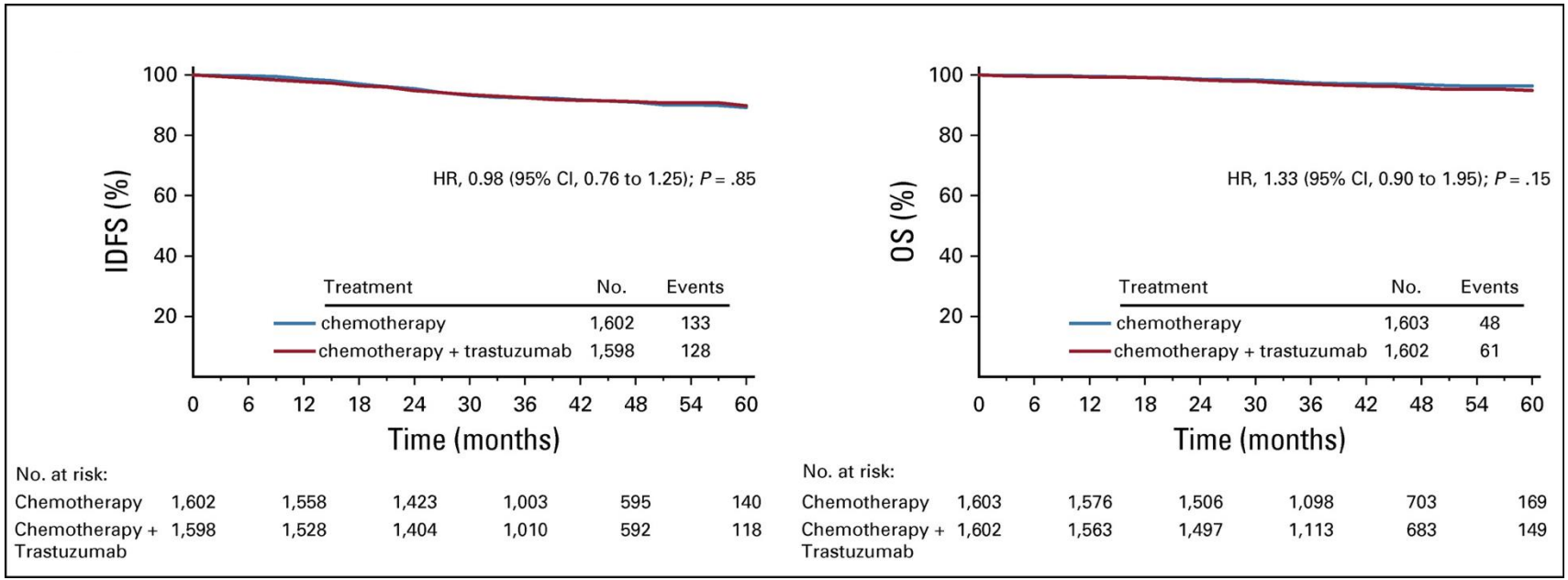
NSABP B-47 phase 3 trial

To understand whether HER2-blockade could also be helpful in **HER2-negative tumors with detectable HER2 expression**, a large phase 3 trial of adjuvant trastuzumab was conducted



Adapted from: Fehrenbacher L, et al. *J Clin Oncol.* 2020;38(5):444-453.

NSABP B-47 phase 3 trial

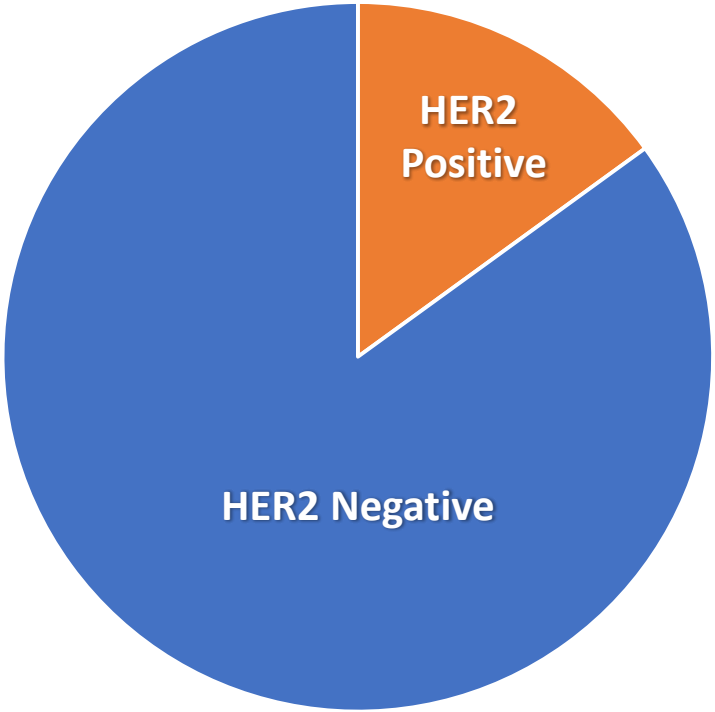


NO BENEFIT of adjuvant trastuzumab in this population

Adapted from: Fehrenbacher L, et al. *J Clin Oncol.* 2020;38(5):444-453.

The “Traditional” HER2 pie chart

Given lack of benefit from trastuzumab, most breast tumors (~80-85%) have been defined **HER2-negative** for decades, despite the presence of detectable HER2 expression



Adapted from Wolff A, et al. *J Clin Oncol.* 2018 10;36(20):2105-2122.

HER2-targeted Agents for HER2+ Breast Cancer

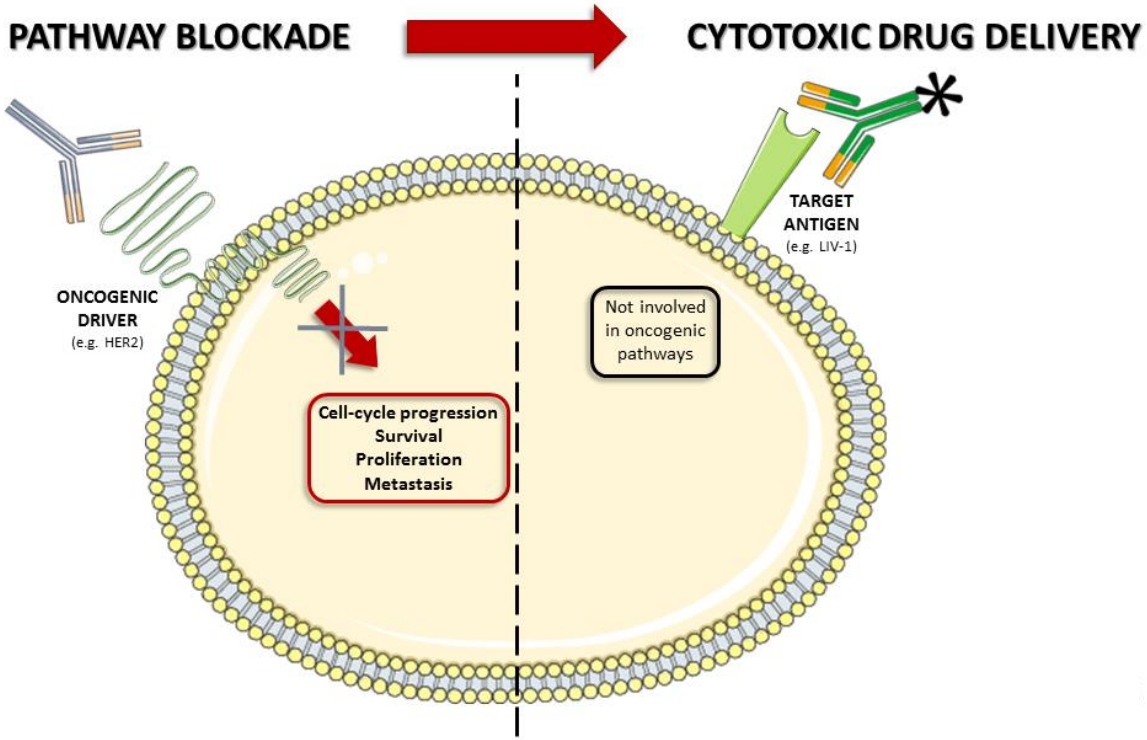
Since the first approval of **trastuzumab** in 1998, **7 additional anti-HER2 agents** have been approved by the FDA and EMA for the treatment of **HER2-positive** breast cancer

- TRASTUZUMAB
- PERTUZUMAB
- LAPATINIB
- TRASTUZUMAB EMTANSINE
- TUCATINIB
- NERATINIB
- TRASTUZUMAB DERUXTECAN
- MARGETUXIMAB

FDA. Accessed March 19, 2024. https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases.

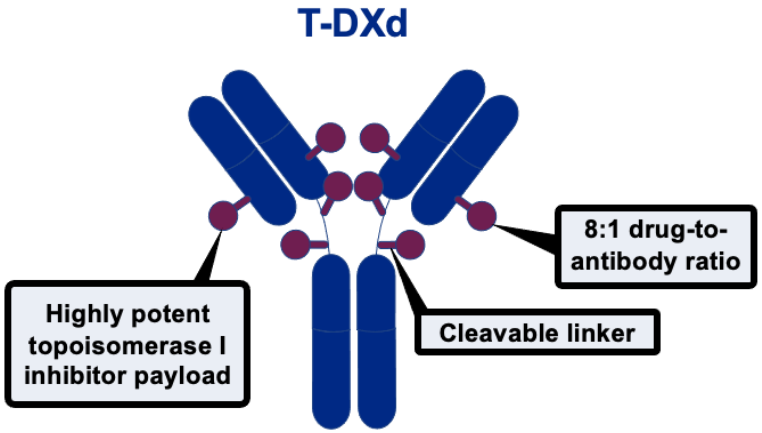
HER2-low: Distinct Entity?

- The development of **novel anti-HER2 ADCs** has recently challenged this paradigm, with **activity in tumors canonically defined HER2-negative**
- **No distinct biology**
- **No distinct prognosis**
- **No distinct genomic profile**

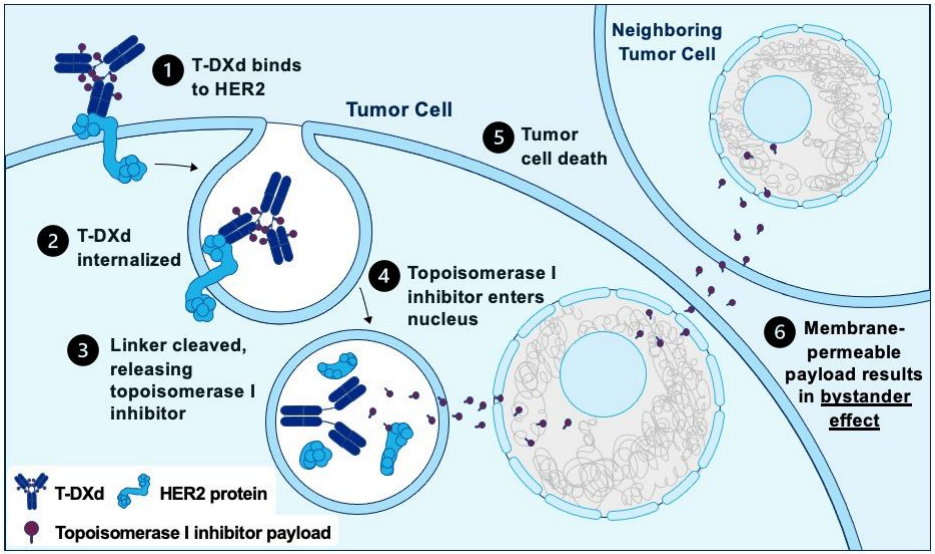


Tarantino P, et al. *Expert Opin Biol Ther*. 2020;20(9):1009-1024.

Trastuzumab deruxtecan (T-DXd)



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect



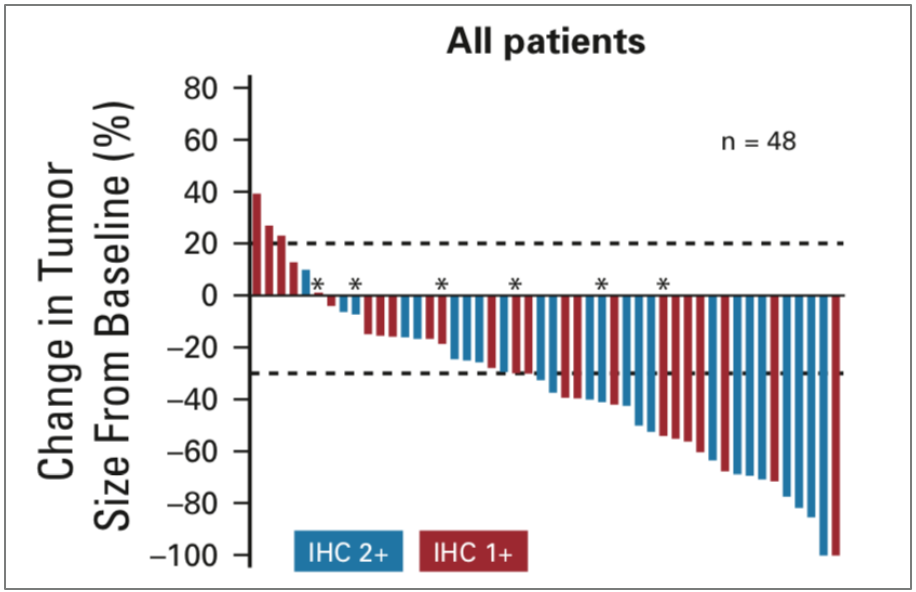
Modi S, et al. ASCO Annual Meeting 2022

J101 Phase 1 Trial: T-DXd for HER2-low MBC

First presented at ASCO 2018, results from a Phase 1b study of **trastuzumab deruxtecan (T-DXd)** suggested activity in HER2-low BC.

Among 54 highly pre-treated (median 7.5) mBC patients with **HER2 IHC 1+ or 2+/FISH-**:

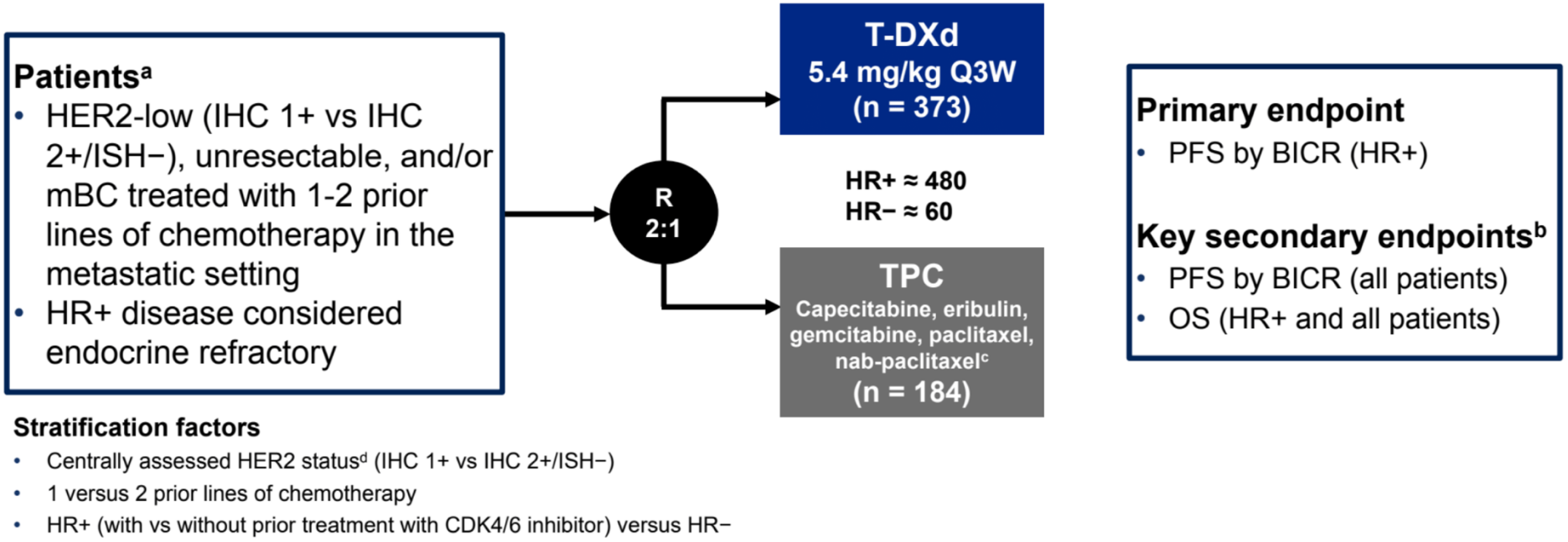
- ORR 37%, responses in IHC 1+ and 2+
- mPFS 11 months



IHC = immunohistochemistry.

Modi S, et al. *J Clin Oncol.* 2020;38:1887–1896.

DESTINY-Breast04 phase 3 trial: T-DXd vs chemo for HER2-low MBC



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−

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DESTINY Breast 04 Patient Characteristics

90% HR+ (n=499), 10% TNBC (n=58)

Median of 2 prior lines of ET and 1 chemo

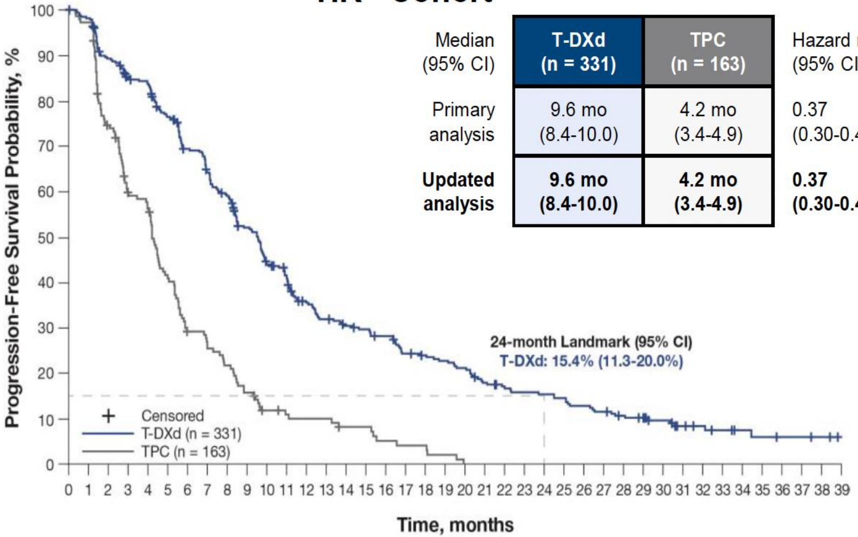
	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
Asia	128 (39)	60 (37)	147 (39)	66 (36)
North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
1+	193 (58)	95 (58)	215 (58)	106 (58)
2+/ISH−	138 (42)	68 (42)	158 (42)	78 (42)
ECOG performance status, %				
0	187 (56)	95 (58)	200 (54)	105 (57)
1	144 (44)	68 (42)	173 (46)	79 (43)
Hormone receptor,[a] n (%)				
Positive	328 (99)	162 (99)	333 (89)	166 (90)
Negative	3 (1)	1 (1)	40 (11)	18 (10)
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)
Lung metastases at baseline, n (%)	98 (30)	58 (36)	120 (32)	63 (34)
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)

NCT03734029.
Accessed March 31, 2023.
https://clinicaltrials.gov/ct2/show/NCT03734029.

DESTINY-Breast04 phase 3 trial: Updated PFS

HR+ Cohort

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)**

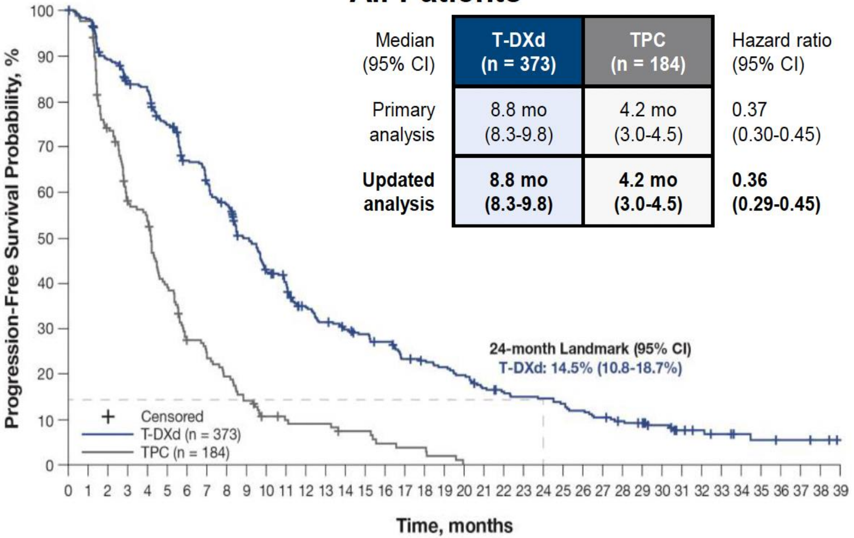


Patients still at risk:

T-DXd (n = 331)	331	323	290	272	267	241	215	198	181	154	129	119	98	88	82	79	74	63	60	57	53	44	40	37	36	34	30	27	23	21	16	11	9	7	5	4	3	3	2	0
TPC (n = 163)	163	143	107	83	78	56	39	34	29	21	14	12	11	11	8	8	5	4	4	2	0																			

All Patients

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)**



Patients still at risk:

T-DXd (n = 373)	373	364	327	304	297	267	234	216	198	166	140	130	107	97	90	85	79	67	64	60	55	46	42	39	38	35	31	27	23	21	16	11	9	7	5	4	3	3	2	0
TPC (n = 184)	184	163	121	92	85	61	41	35	29	21	14	12	11	11	8	8	5	4	4	2	0																			

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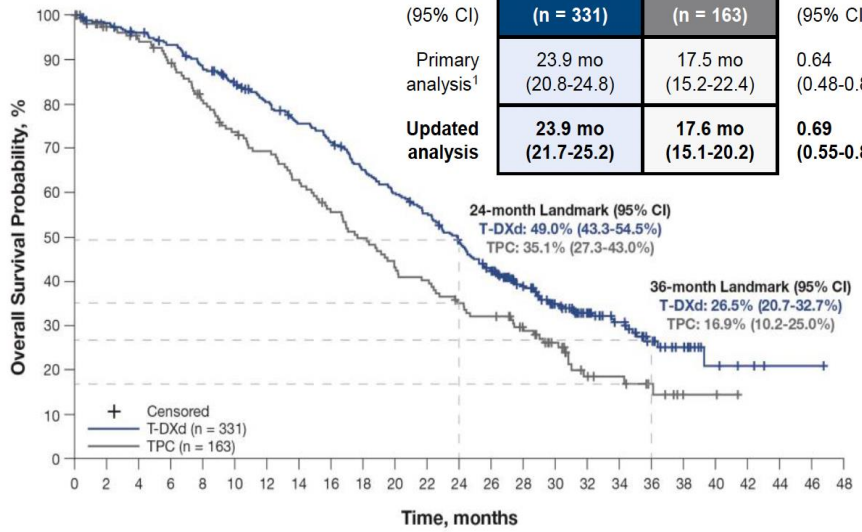
DESTINY-Breast04 phase 3 trial: Updated OS

HR+ Cohort

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)**



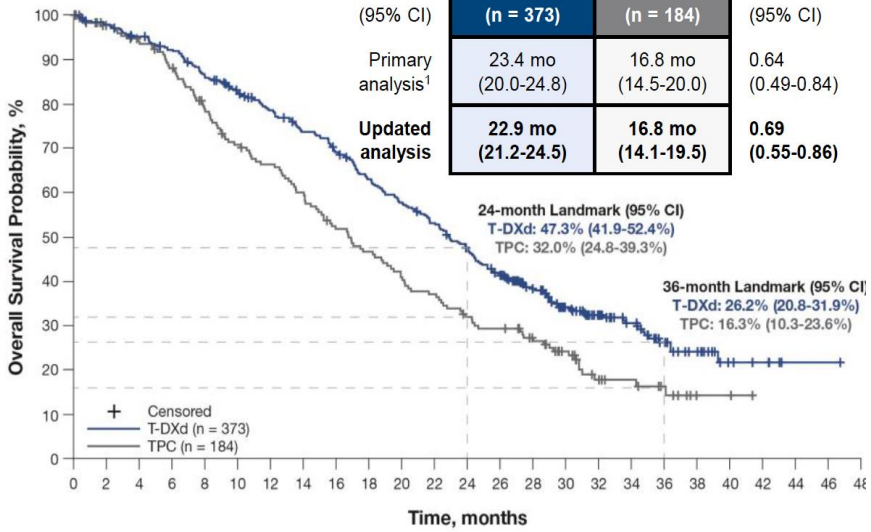
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 155 147 135 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 103 97 96 92 87 82 76 71 68 64 59 56 55 50 47 43 43 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

All Patients

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 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**



Patients still at risk:

T-DXd (n = 373) 373 366 363 355 350 342 337 325 314 308 295 285 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

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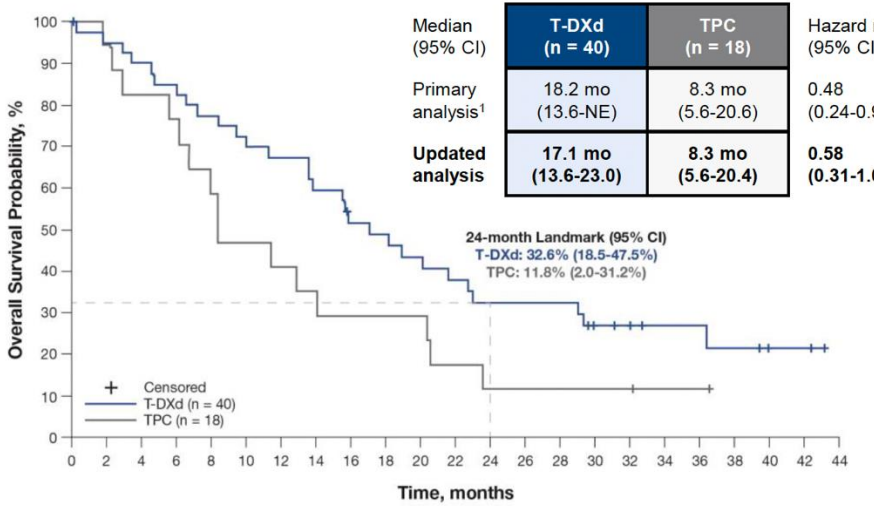
DESTINY-Breast 04 phase 3 trial: activity in TNBC (i.e. HR-/HER2-low)

Overall Survival

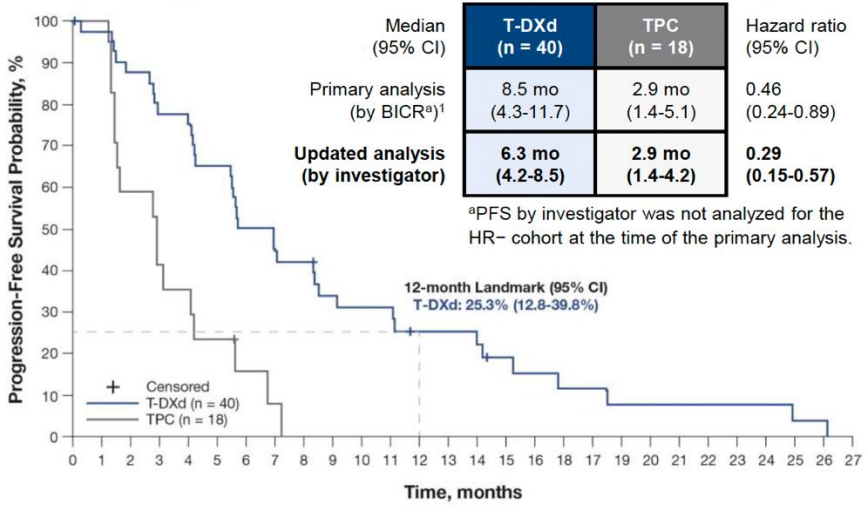


Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**

Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	12	8	7	5	5	4	2	2	0
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	2	1	1	0	0	0	0

Progression-Free Survival (by Investigator)



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.

Patients still at risk:

T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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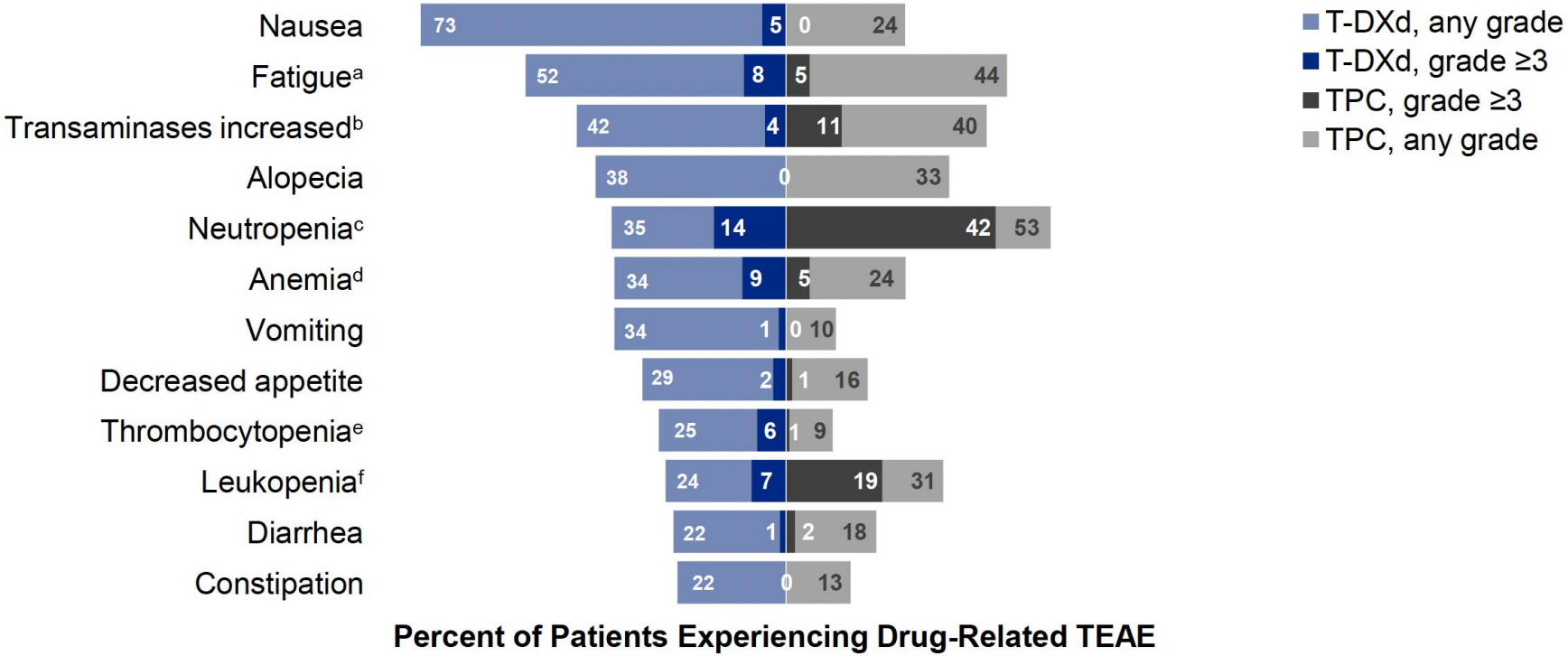
DESTINY-Breast 04 phase 3 trial: Adverse Events

Drug-Related TEAEs in ≥20% of Patients



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Anti-emetic prophylaxis with T-DXd

The SmPC lacks specific antiemetic guidance, however other resources are available with more specific guidance[1]

Such guidelines include:[2,3]

ASCO

MASCC

ESMO

Insights from an expert panel recommend:[4]

A thorough evaluation of individual patient characteristics and clinical history is crucial to tailor treatment and optimise efficacy while limiting toxicities

In select patients with increased risk of emesis (e.g., characteristics and site of the tumour, patient age and gender, constipation, prior nausea induced by chemotherapy), antiemetic prophylaxis from the first cycle should be started with a **three-drug regimen (including NK-1 receptor blockers)**

In the case of anything less than an optimal control of emesis during the first cycle using the DEX + 5-HT_3 regime, attempts to introduce minor modifications should be discouraged. Instead, treatment should be immediately escalated before the second cycle using a **three-drug regimen (including NK-1 blockers)**

5-HT_3=5-hydroxytryptamine 3; ASCO=American Society of Clinical Oncology; DEX=dexamethasone; ESMO=European Society for Medical Oncology; MASCC=Multinational Association of Supportive Care in Cancer; NK-1=neurokinin-1; SmPC=summary of product characteristics.

1. EMA. Enhertu® (trastuzumab deruxtecan) SmPC. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf. Accessed September 2022; 2. Hesketh PJ, et al. J Clin Oncol. 2020;38(24):2782-2797; 3. Roila F, et al. Ann Oncol. 2016;27(suppl 5):v119-v133; 4. Bianchini G, et al. Cancers (Basel). 2022;14(4):1022.

Adverse Events of Special Interest

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
ILD/pneumonitis (adjudicated, drug-related), n (%)						
T-DXd (n = 371)	13 (3.5)	24 (6.5)	4 (1.1)[a]	0	4 (1.1)[a]	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction						
Ejection fraction decreased, n (%)						
T-DXd (n = 371)	2 (0.5)	15 (4.0)	1 (0.3)	0	0	18 (4.9)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure, n (%)						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

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Management of ILD: the 5 S rules

1 Screen

- Careful patient selection is warranted before initiating T-DXd to optimize the monitoring strategies based on the baseline risk
- Screening continues during treatment, with regular clinical assessments to exclude signs/symptoms of ILD

2 Scan

- The fundamental diagnostic tools for ILD remain radiological scans, with preference for high-resolution CT scans of the chest
- A baseline scan is recommended, with repeat scans to be performed every 6-12 weeks

3 Synergy

- Minimizing the risk of ILD involves teamwork, which includes educating patients and all the care team, as well as multidisciplinary management once ILD is suspected

4 Suspend Treatment

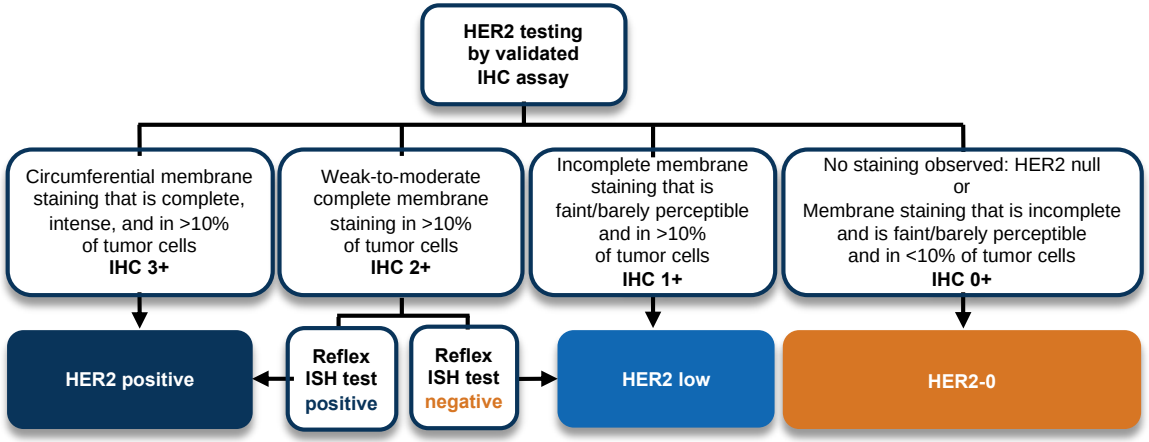
- T-DXd should always be interrupted if ILD is suspected; it can only be restarted in the case of asymptomatic ILD that fully resolves

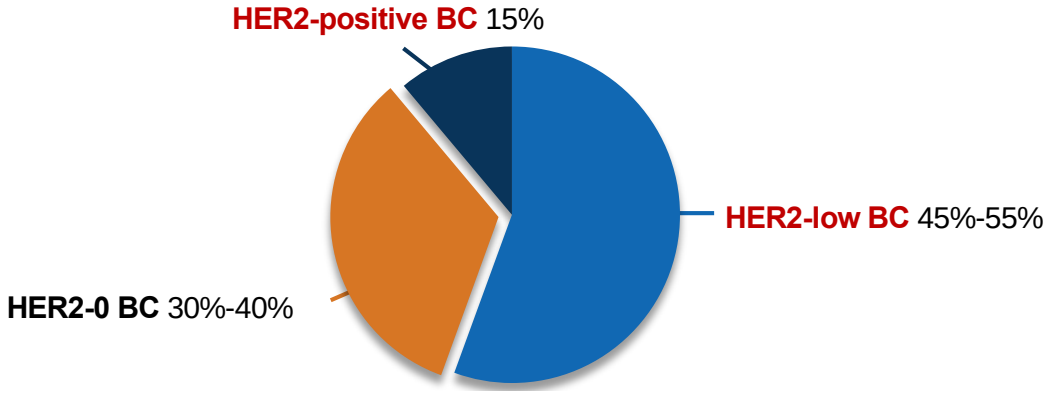
5 Steroids

- The mainstay for treating T-DXd–induced ILD remains corticosteroids, with the dose to be adapted to the toxicity grade

Tarantino P. et al, JCO Onc Prac 2023

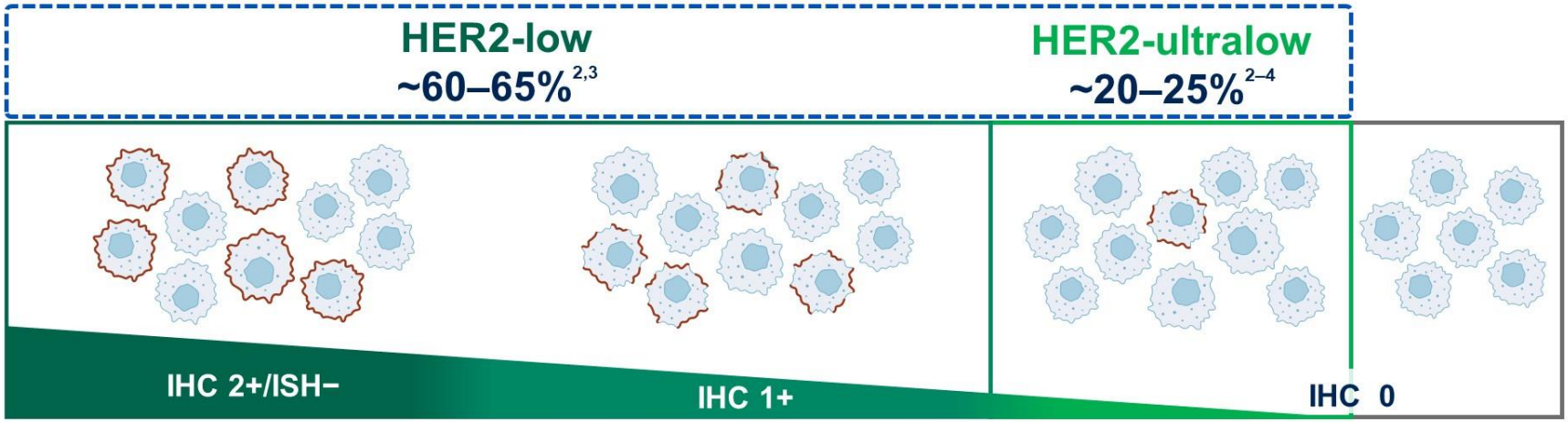
Most patients with MBC are currently eligible for T-DXd





Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-1962.

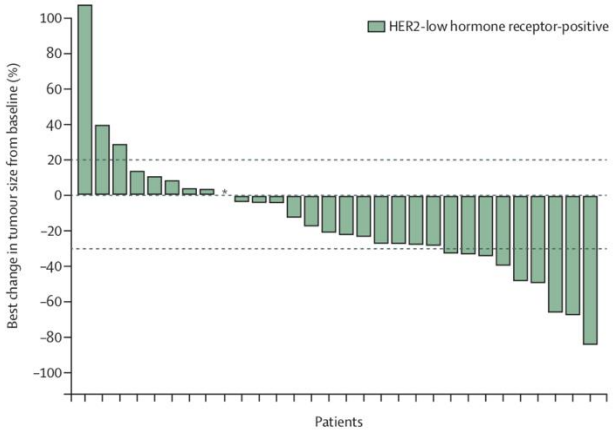
Hormone receptor positive breast cancers express a wide range of HER2



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

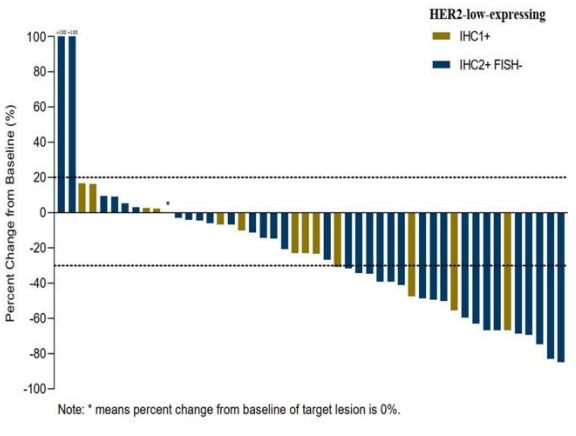
Multiple additional HER2 ADCs are showing promising activity in HER2-low MBC

Trastuzumab duocarmazine



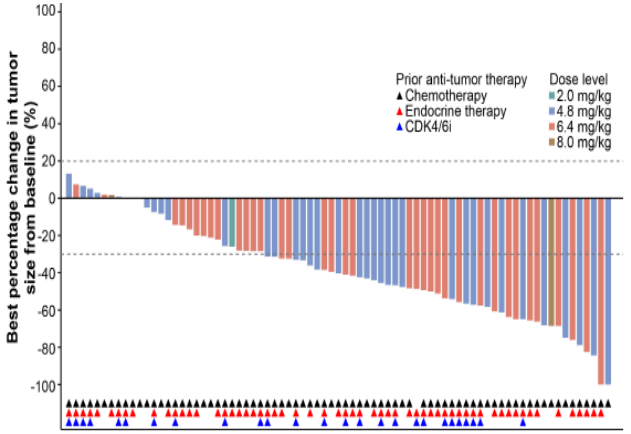
49 patients with HER2-low mBC: ORR 32%

Disitamab Vedotin



48 patients with HER2-low mBC: ORR 40%

Trastuzumab Rezetecan



77 patients with HER2-low mBC: ORR 60%

Banerji U, et al. Lancet Oncol. 2019;20(8):1124–1135; Wang J, et al. Presented at ASCO 2021; Zhang T. AACR 2023

DESTINY-Breast06 Study design

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

PATIENT POPULATION

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

Prior lines of therapy

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

Stratification factors

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

R 1:1

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

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

Options: capecitabine, nab-paclitaxel, paclitaxel

ENDPOINTS

Primary

- PFS (BICR) in HER2-low

Key secondary

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

Other secondary

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

*Study enrollment was based on central HER2 testing. HER2 status was determined based on the most recent evaluable HER2 IHC sample prior to randomization. HER2-ultralow was defined as faint, partial membrane staining in ≤10% of tumor cells (also known as IHC >0<1+); †HER2-ultralow status as determined per IRT data (note: efficacy analyses in the HER2ultralow 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 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

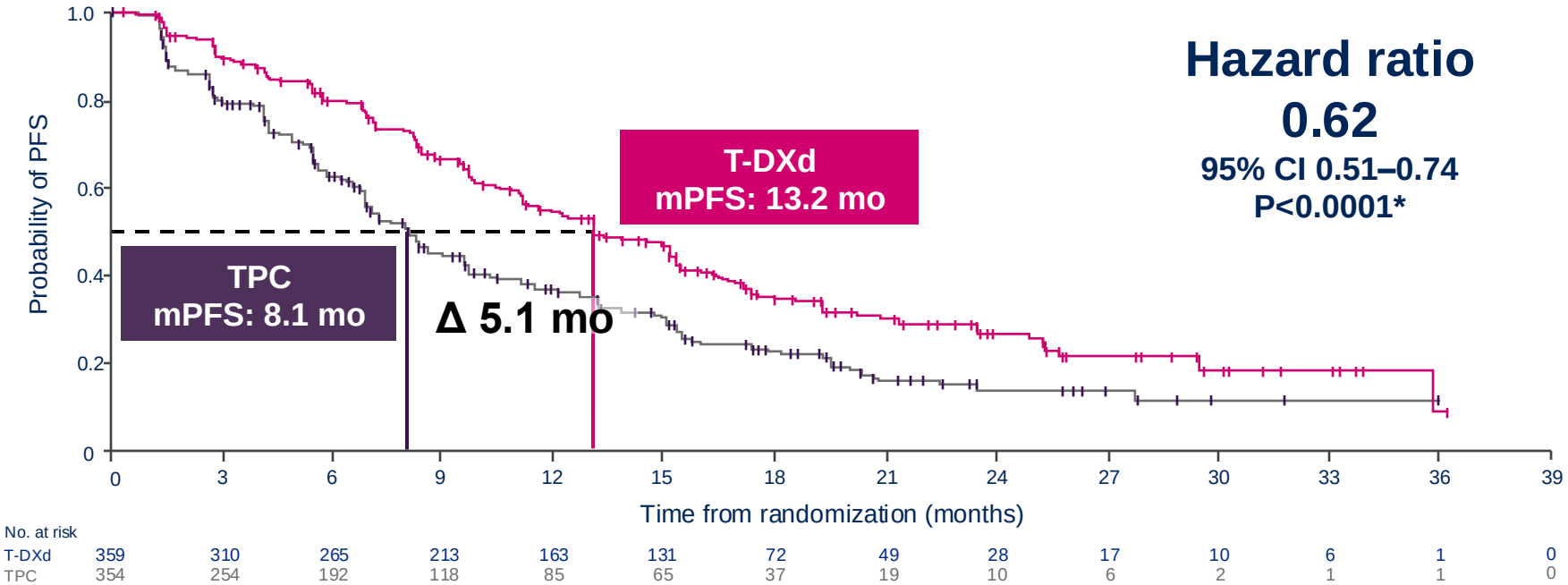
	HER2-low*		ITT (HER2-low and HER2-ultralow)		HER2-ultralow*	
	T-DXd (n=359)	TPC (n=354)	T-DXd (n=436)	TPC (n=430)	T-DXd (n=76)	TPC (n=76)
ET in the metastatic setting						
Lines of ET						
Number of lines, median (range)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)	2.0 (1–4)	2.0 (1–5)
Number of lines, n (%)						
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

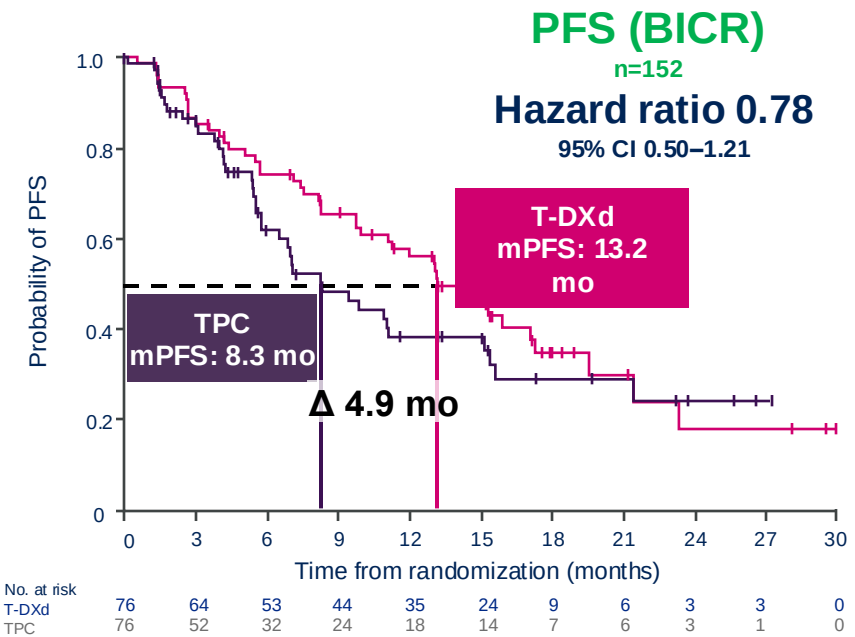
DESTINY- Breast 06: PFS (BICR) in HER2-low: primary endpoint

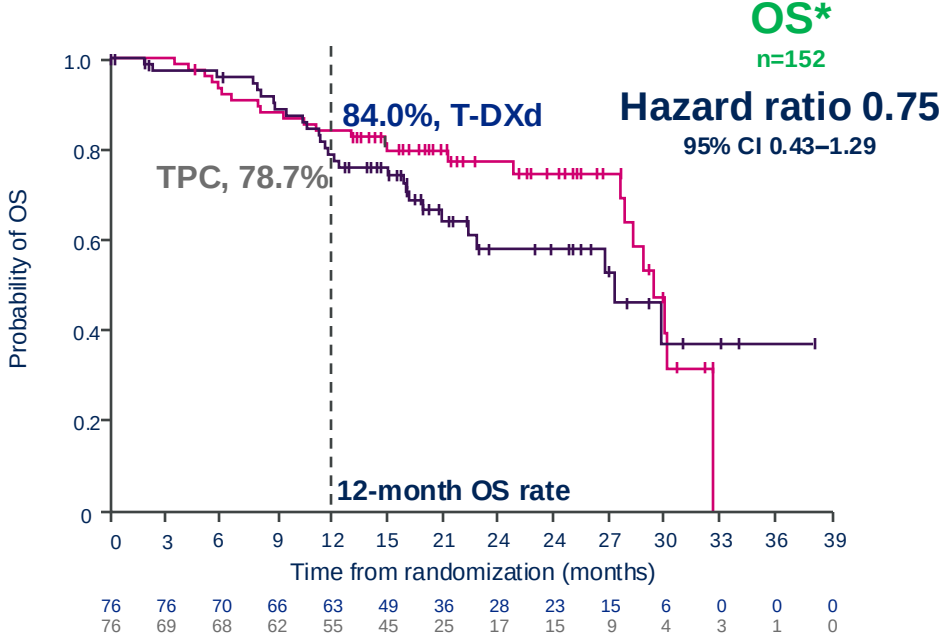
Median of 2 prior lines of ET, 90% with prior CDK4/6i, **no prior chemo**, 85% had visceral disease, 70% relapsed



Curigliano G et al. ASCO 2024; Bardia NEJM 2024

DESTINY Breast 06: PFS and OS 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

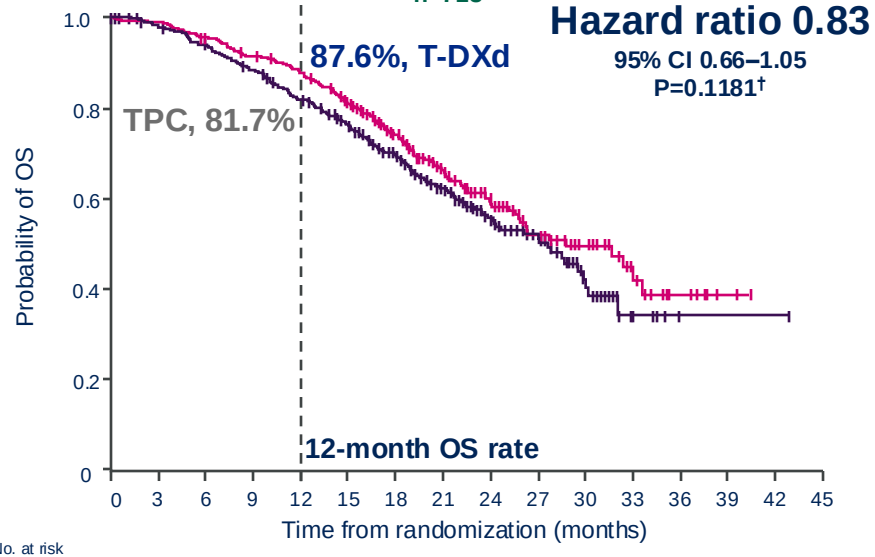
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

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

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

HER2-low*

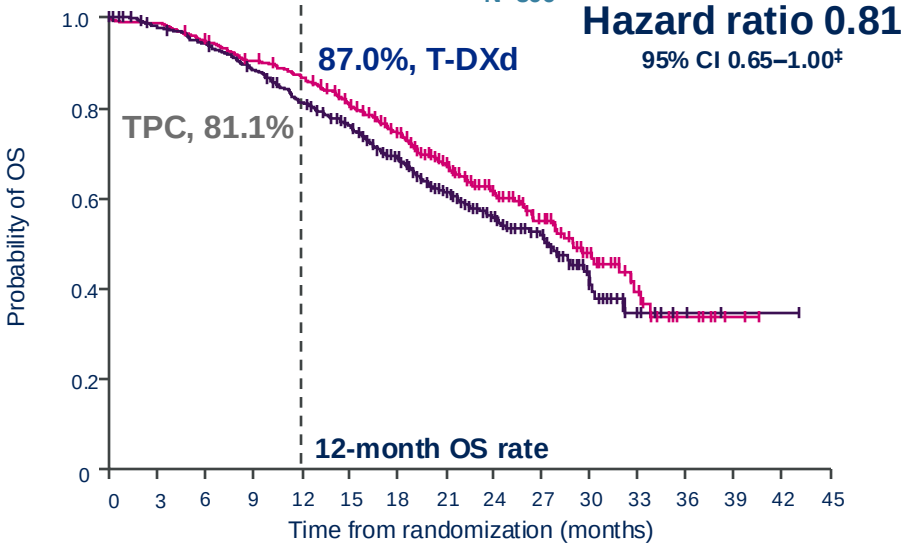
n=713



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

ITT (HER2-low + HER2-ultralow)

N=866



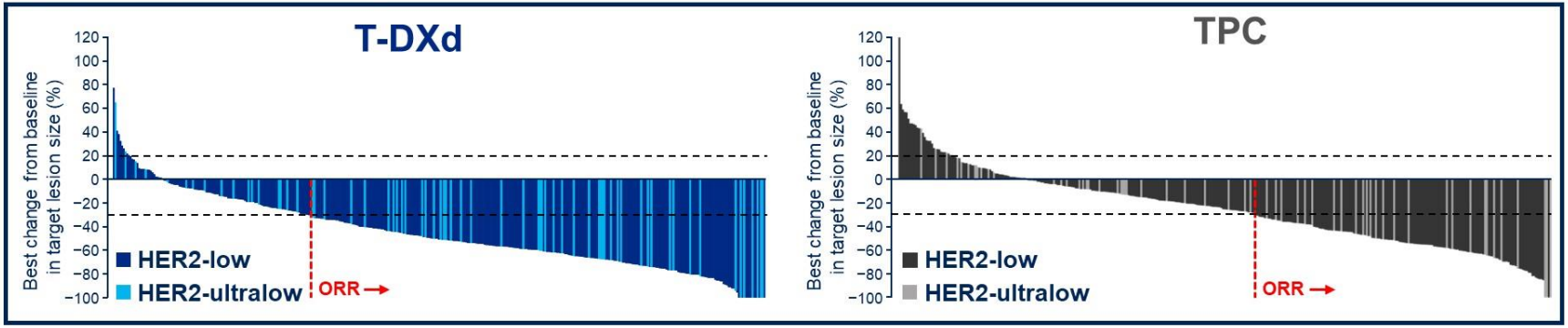
17.9% of patients in the TPC group received T-DXd post treatment discontinuation (ITT)

*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

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

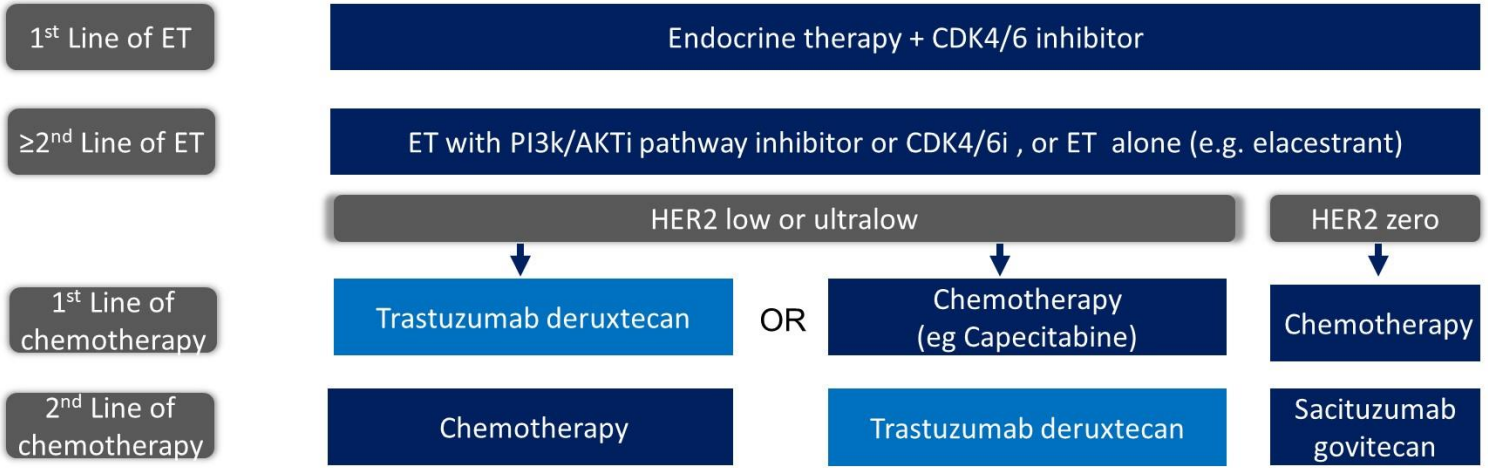
Antitumor activity



	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

Approach to therapy for metastatic hormone receptor positive breast cancer



Factors that could help choose 1L vs 2L →

Symptomatic disease Yes/No

Primary *endocrine resistant Yes/No*

Short interval after adj chemotherapy Yes/No

Patient preference

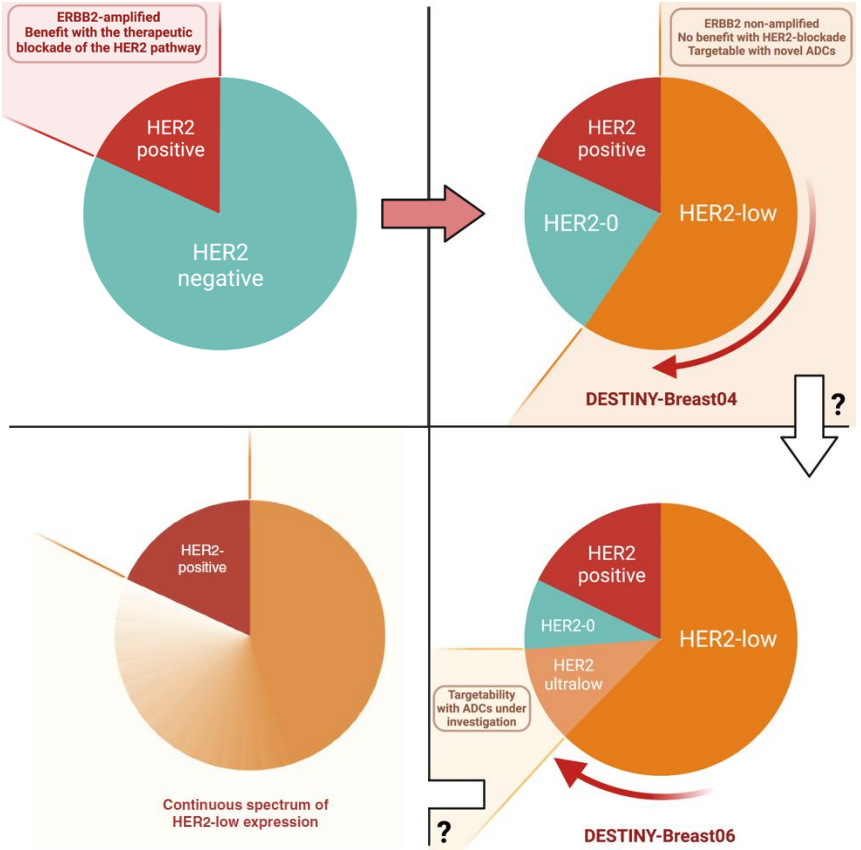
The expanding pie chart of HER2 targetability

Since DESTINY-Breast06 is positive, >90% of all patients with HR+ MBC may be considered eligible for T-DXd

So... should we even test for HER2?

YES!

For 3 main reasons

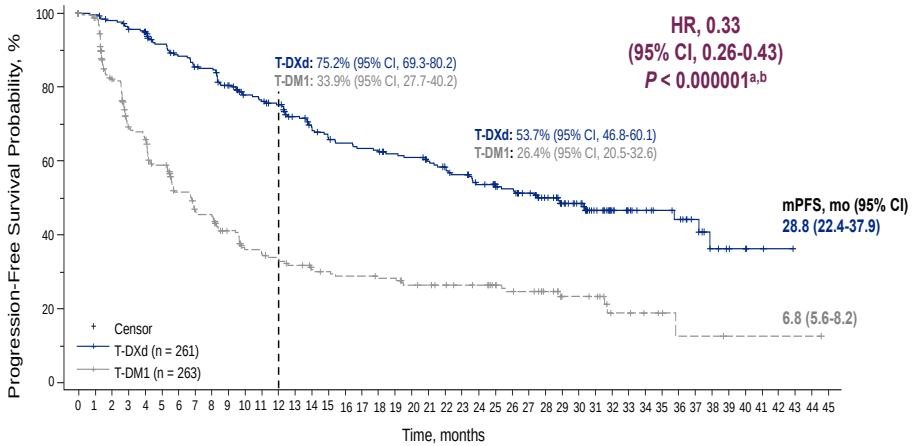


Tarantino P et al. Cancer Discovery 2022

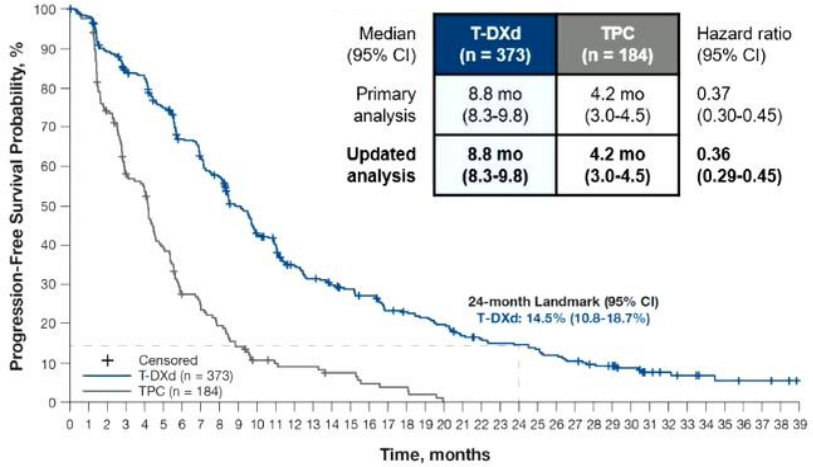
1. To distinguish HER2-positive from other tumors

T-DXd clearly has a **differential activity in HER2+ vs. non-HER2+ tumors**. In addition, **7 more anti-HER2 drugs are approved for the 15% of patients with HER2+ disease**. This makes it critical to understand if patients have HER2+ (overexpressing) or non-HER2+ disease.

DB03 (HER2+) – mPFS with T-DXd: 28.8 months



DB04 (HER2-low) – mPFS with T-DXd: 8.8 months

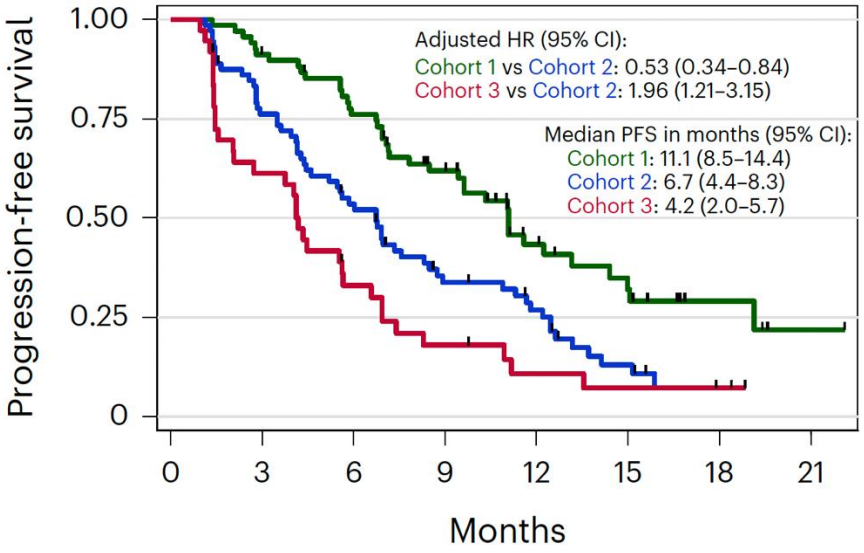


Hurvitz S et al. Lancet 2023; Modi S et al. ESMO 2023

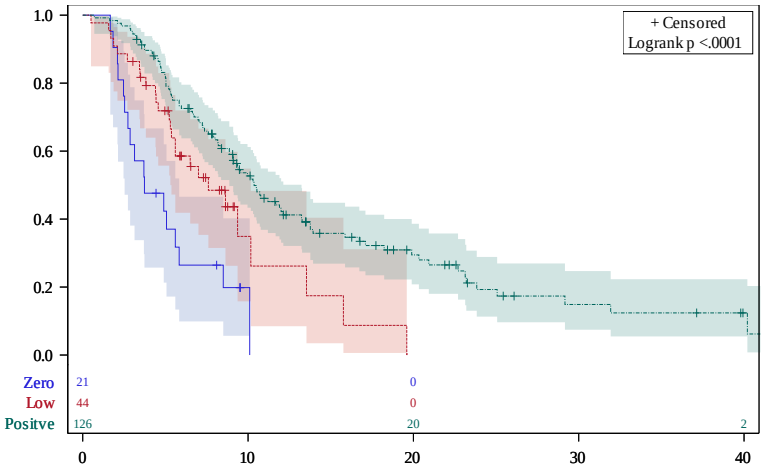
2. Even within HER2-negative tumors, there may be a differential activity with different HER2 expressions

Both the **DAISY phase 2 trial** and our **real-world DFCI/Duke cohort** highlighted a difference in the activity of T-DXd among patients with **HER2-low** (**PFS 7-8 months**) and **HER2-0 MBC** (**PFS ~4 months**)

DAISY phase 2 trial



RW outcomes at DFCI/Duke



MEDIAN TTNT WITH T-DXd WAS:

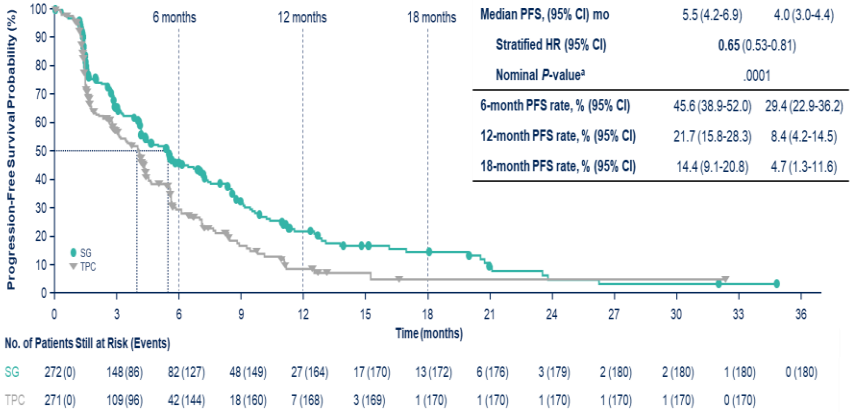
- 10.4 months for **HER2+**
- 7.6 months for **HER2-low**
- 3.7 months for **HER2-0**

Mosele F et al. Nat Med 2023; Tarantino et al. SABCS 2023

3. An expanding deck of other ADCs are becoming available in case of HER2-0 disease

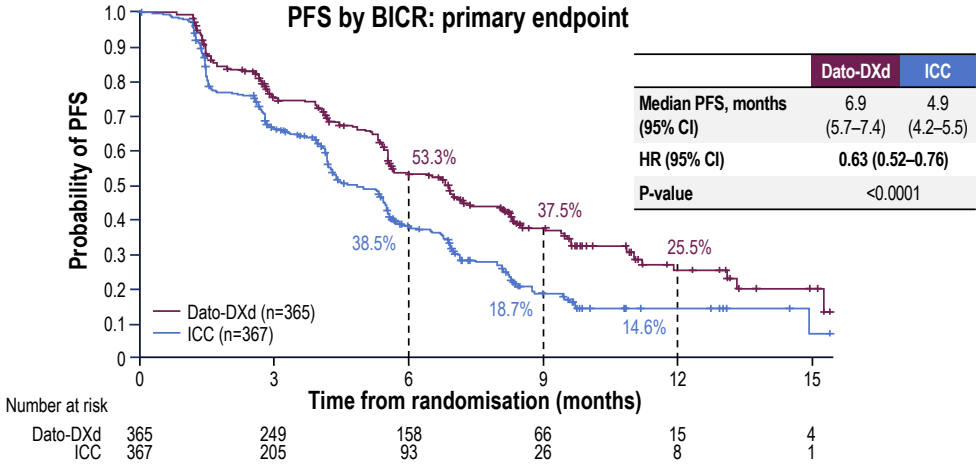
Sacituzumab govitecan is approved for TNBC and HR+ MBC. **Datopotamab deruxtecan** may also be approveved for HR+ MBC. Dozens of additional promising ADCs are in early and late phase testing

TROPiCS-02 phase 3 trial



BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	0.65 (0.53-0.81)	
Nominal *P*-value[a]	.0001	
6-month PFS rate, % (95% CI)	45.6 (38.9-52.0)	29.4 (22.9-36.2)
12-month PFS rate, % (95% CI)	21.7 (15.8-28.3)	8.4 (4.2-14.5)
18-month PFS rate, % (95% CI)	14.4 (9.1-20.8)	4.7 (1.3-11.6)

TROPION-Breast01 phase 3 trial



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	0.63 (0.52–0.76)	
P-value	<0.0001	

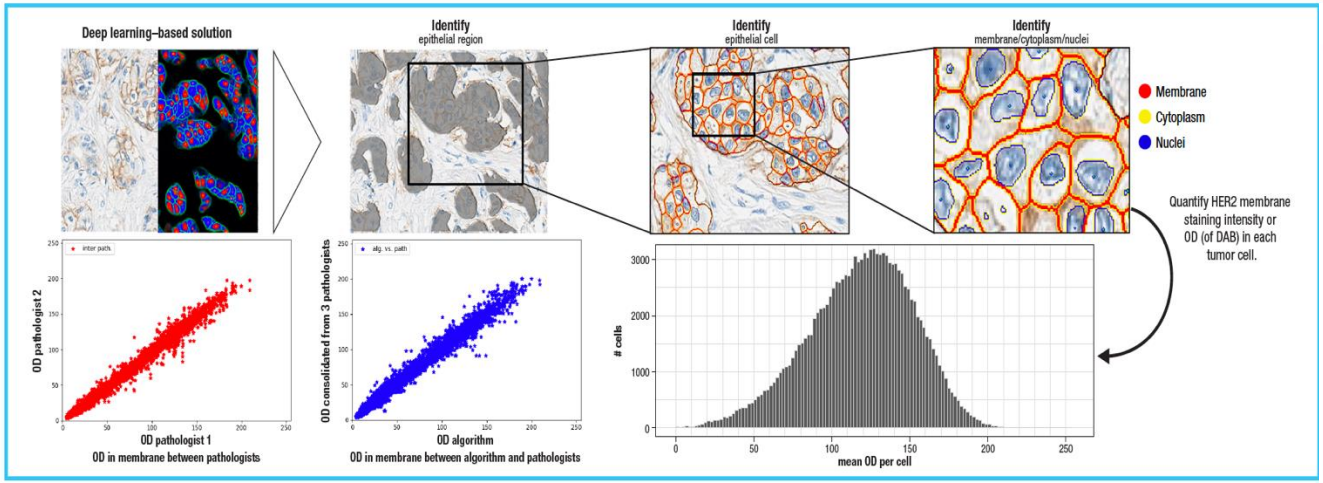
Tolaney SM et al. ASCO 2023; Bardia A. et al ESMO 2023

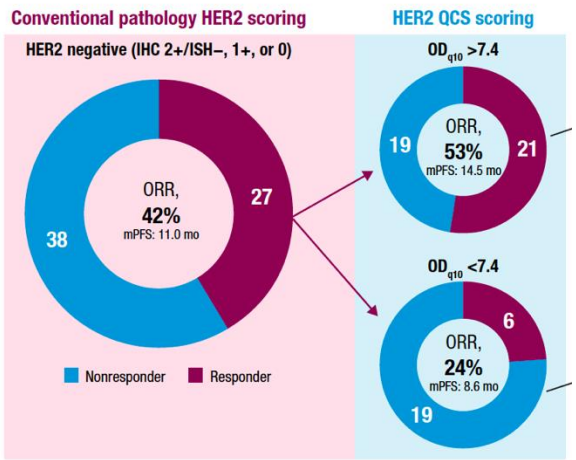
Novel assays may improve HER2 testing

To overcome challenges with IHC testing, multiple **novel HER2 testing strategies** are being investigated.

When applied to the J101 trial of T-DXd in HER2-low MBC, HER2 digital pathology assessment with **QCS** was able to stratify patients in two subgroup with distinct ORR (53% vs 24%) and PFS (14.5 mo vs 8.6 mo)

Additional assays being developed include HER2 quantitative assessment with **qIF**, **mass spectrometry**, **RPPA**, **RT-qPCR**, among others.





Gustavson M. et al. SABCS 2020; Kapil et al Sci Rep. 2024 May 27;14(1):12129

Conclusion

- Up to **70%** of patients with MBC are currently **eligible for T-DXd (**HER2+ or HER2-low). This number may raise to >90% if DB06 is is approved in HER2-ultralow MBC.
- **Testing for HER2 could remain critical**, since it allows to identify HER2+ tumors (distinct biology), stratify different levels of benefit from HER2 ADCs, and prioritize patients for the right therapies
- Concomitantly, the emergence of **quantitative HER2 assays** may refine our HER2 testing categories, ultimately enhancing treatment tailoring with anti-HER2 ADCs
- Dozens of novel ADCs currently in testing are expected to further improve outcomes for MBC and create opportunities for treatment tailoring

Acknowledgements

- Breast Medicine and Early Drug Development Service
- Patients and their families who inspire us everyday!

@jhaveri_komal