HER2-Low breast cancers – possibilities and challenges

PROF DAVID CAMERON

UNIVERSITY OF EDINBURGH

CHAIR BREAST INTERNATIONAL GROUP

conflicts

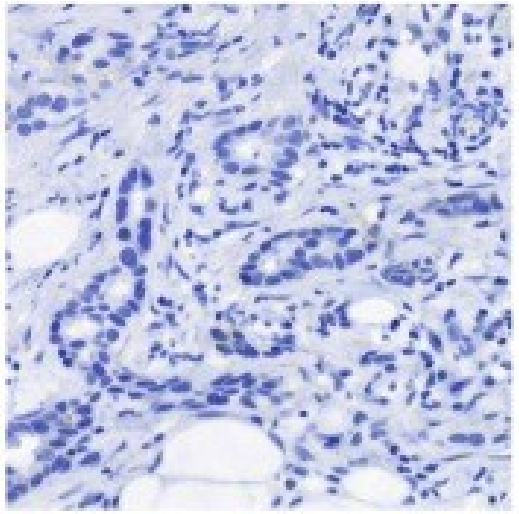
All non-personal (any money goes to institution)

Relevant ones:

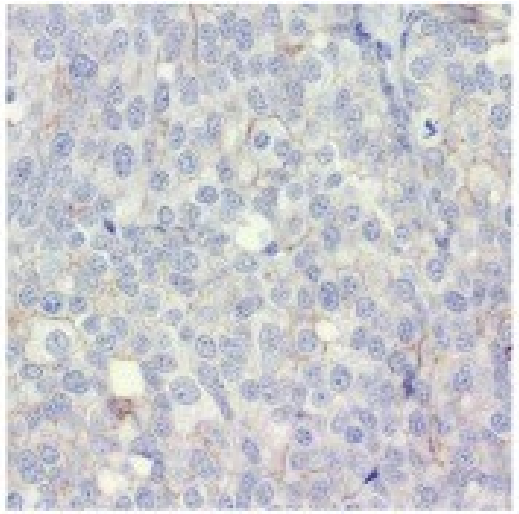
- Roche
- Gilead
- PUMA
- Novartis
- GSK
- SeaGen
- Daiichi-Sankyo
- Astra-Zeneca
- Synthon

HER2 in breast cancer

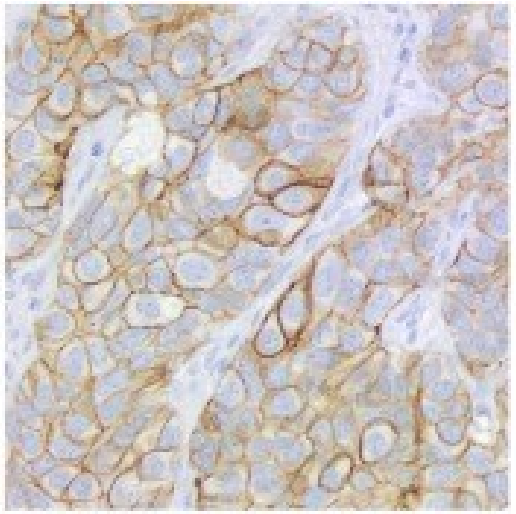
- High levels associated with poorer outcomes
- Active downstream signalling
  - Reduces endocrine sensitivity
- High levels found in 15-20% of breast cancers
  - Lower rates in screen-detected cancers
- Pathologists work hard to identify the Over-expressing cancers
  - Report HER2 negative for any level of expression BELOW amplified……
    - HER2 0, 1 and 2 can have very varying levels of protein on the cell surface, and varying heterogeneity….
    - But all called HER2 Negative



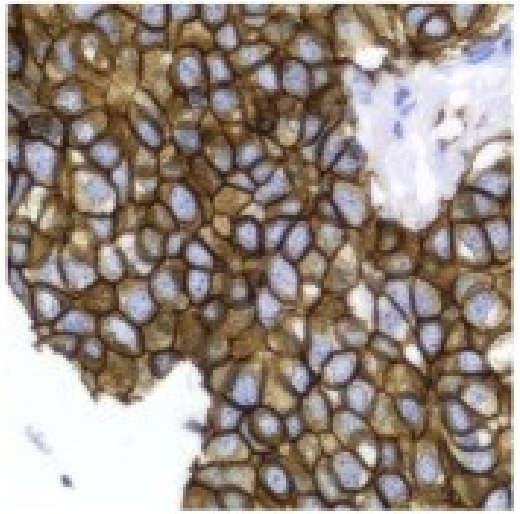
HER2
SCORE 0



HER2
SCORE 1+



HER2
SCORE 2+



HER2
SCORE 3+

ISH

Not Amp | Equivocal | Amp

HER2-neg carcinomas

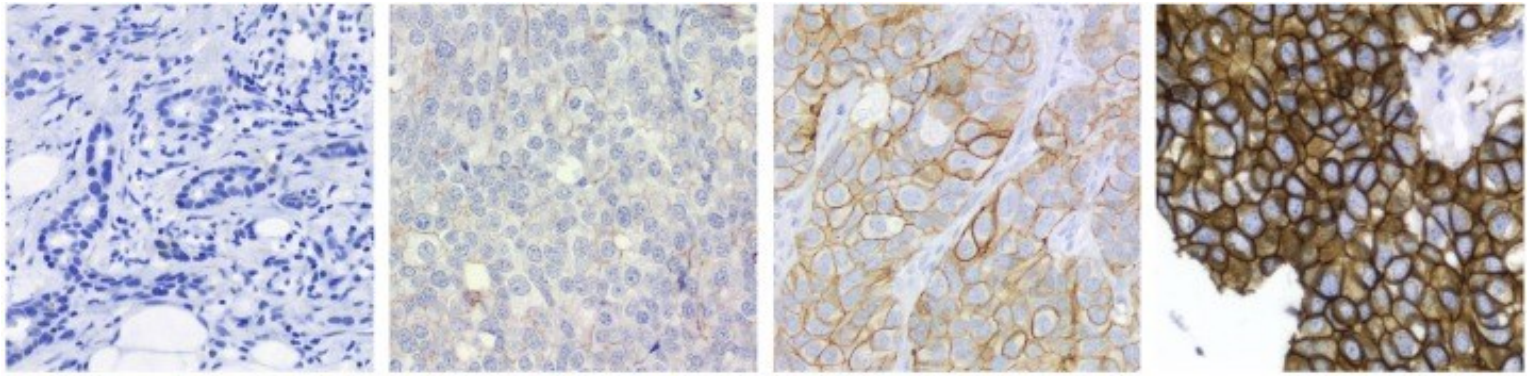
Spectrum of HER2-low carcinomas

HER2-pos carcinomas

No benefit from anti-HER2 agents, lack of HER2 expression and HER2 pathway activation

Possible benefit from new generation of ADCs attaching to the HER2 receptors present on the cell membrane and then delivering the chemotherapeutic compounds

Benefit from anti-HER2 agents blocking addition to HER2 pathway hyperactivation stemming from HER2 overexpression and amplification



HER2 SCORE 0 | HER2 SCORE 1+ | HER2 SCORE 2+ | HER2 SCORE 3+

ISH

Not Amp | Equivocal | Amp

HER2-neg carcinomas

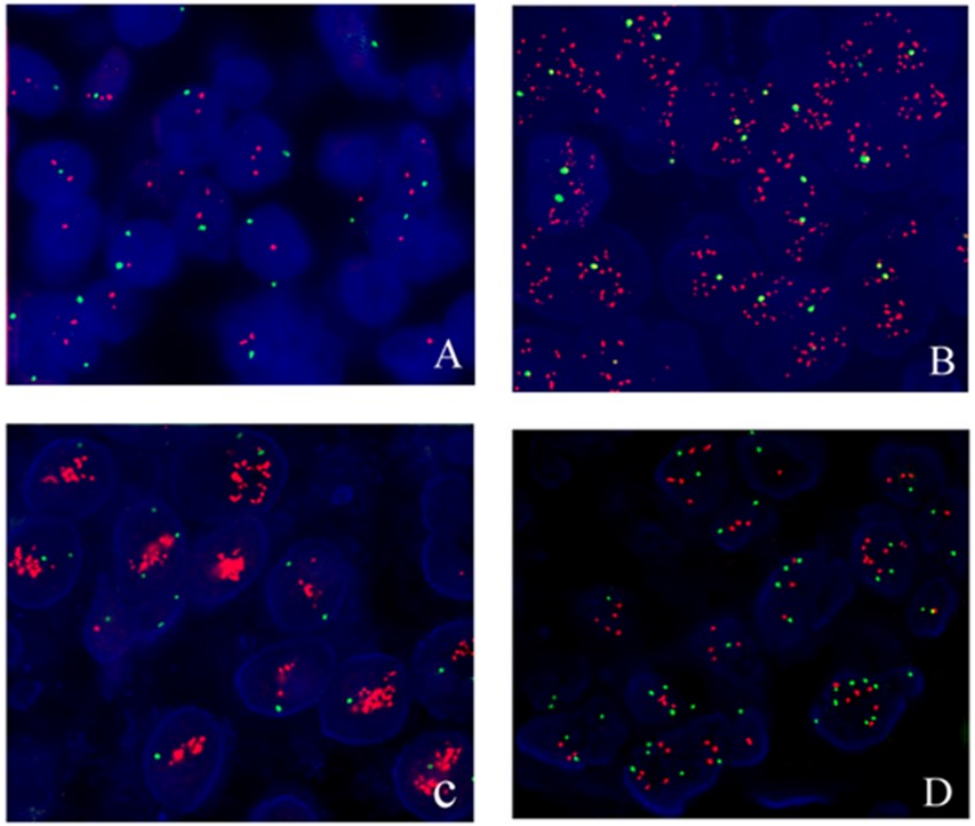
No benefit from anti-HER2 agents, lack of HER2 expression and HER2 pathway activation

Spectrum of HER2-low carcinomas

Possible benefit from new generation of ADCs attaching to the HER2 receptors present on the cell membrane and then delivering the chemotherapeutic compounds

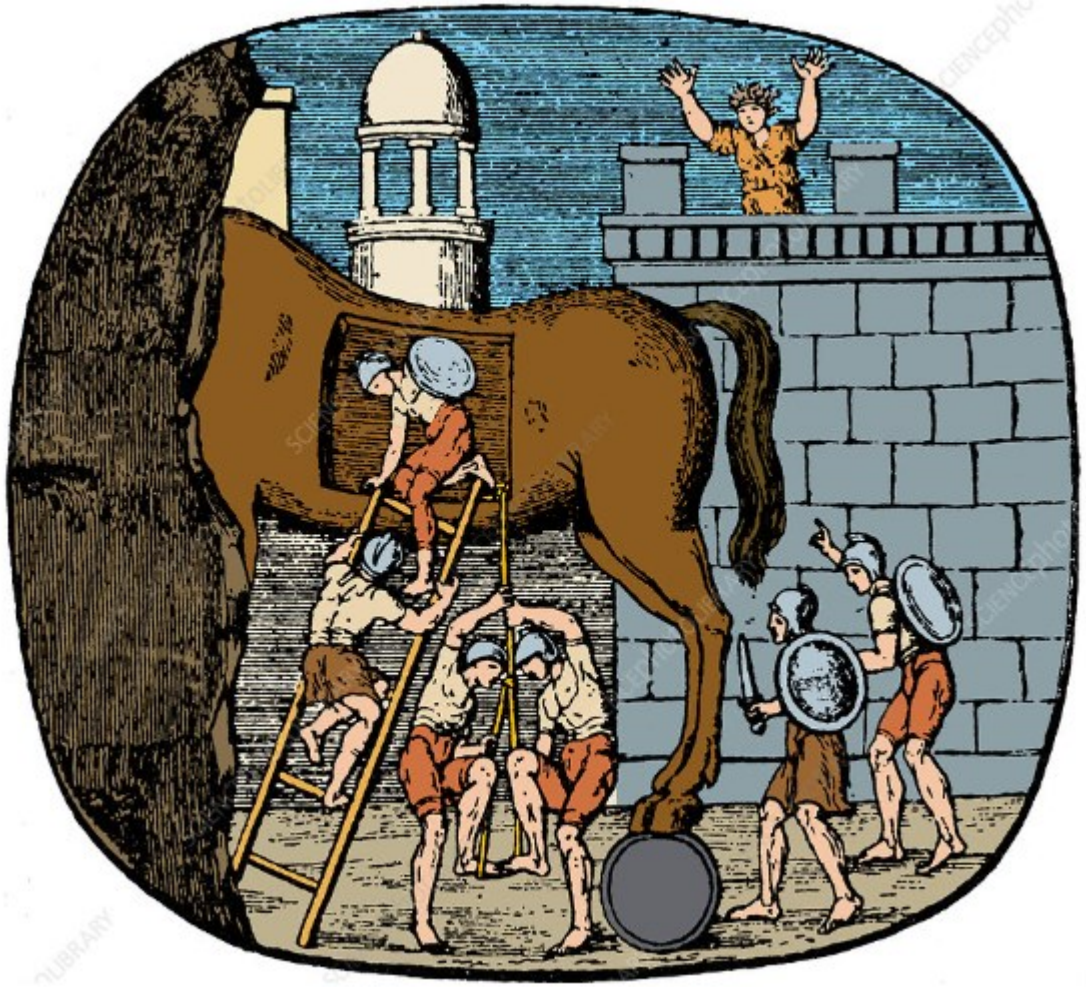
HER2-pos carcinomas

Benefit from anti-HER2 agents blocking addition to HER2 pathway hyperactivation stemming from HER2 overexpression and amplification

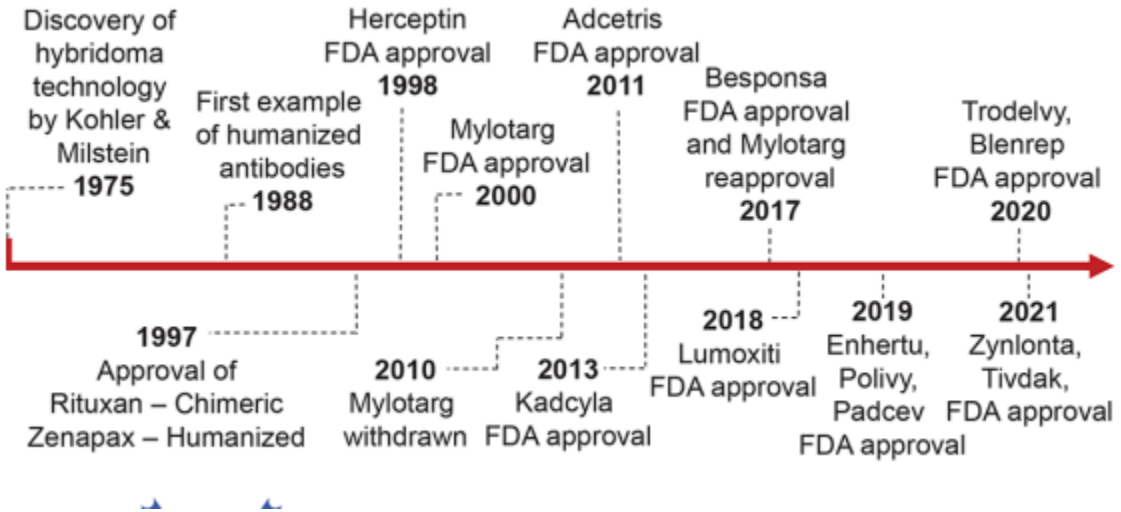


Non-HER2 Positive didn’t seem to matter

UNTIL NOW……??



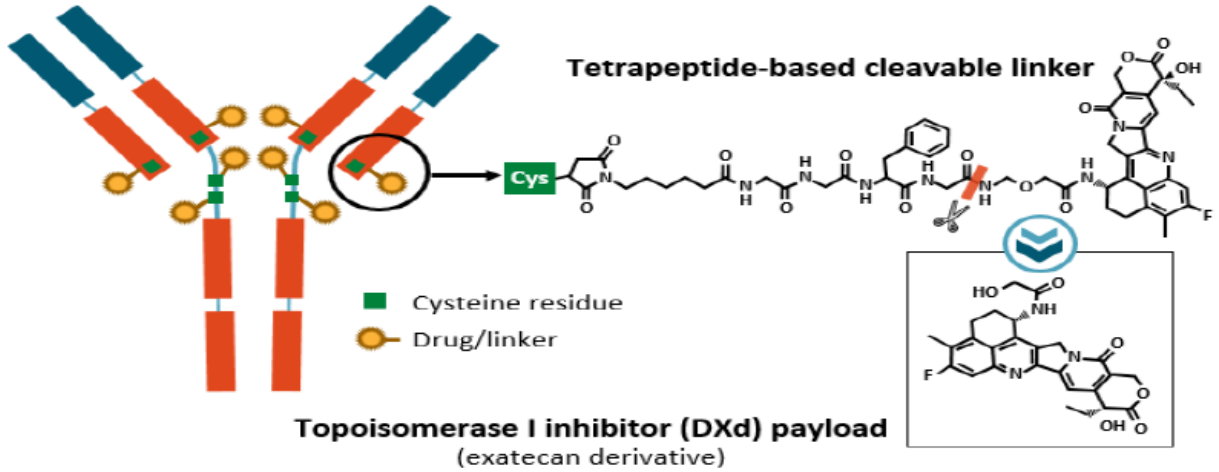
History of Trojan biologicals (ADCs)



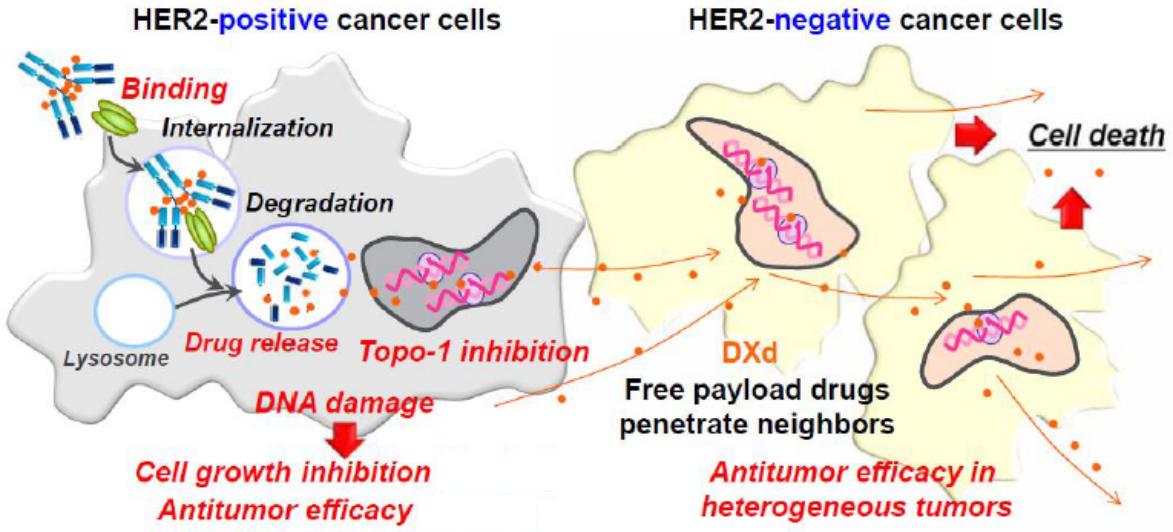
T-DXd: Structure and MoA

• Structure[1]

- **Antibody:** Monoclonal humanized anti-Her2 IgG1
- **Linker:** Cleavable linker (Gly-Gly-Phe-Gly)
- **Payload:** Topoisomerase I inhibitor
- **DAR:** ~8:1



• Mechanism of action (MoA)[2]



Activity was seen in HER2-low cancers in early phase trials….

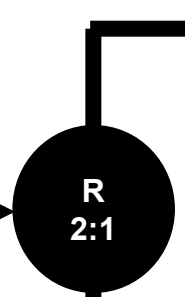
HER2: human epidermal growth factor receptor 2; IgG1: immunoglobulin G1; Gly: glycine; Phe: phenylalanine; DAR: drug-antibody ratio. [1]Nagai Y. et al, Xenobiotica 2019. [2]Image from Daiichi Sankyo

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

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



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

HR+ ≈ 480
HR− ≈ 60

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

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−) (ER was LOCAL)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

DESTINY-Breast04: Statistical Analysis and Hierarchical Testing

Hierarchical testing

PFS in HR+

↓

PFS in all patients

↓

OS in HR+

↓

OS in all patients

Primary analysis for PFS by BICR (planned after at least 318 events)

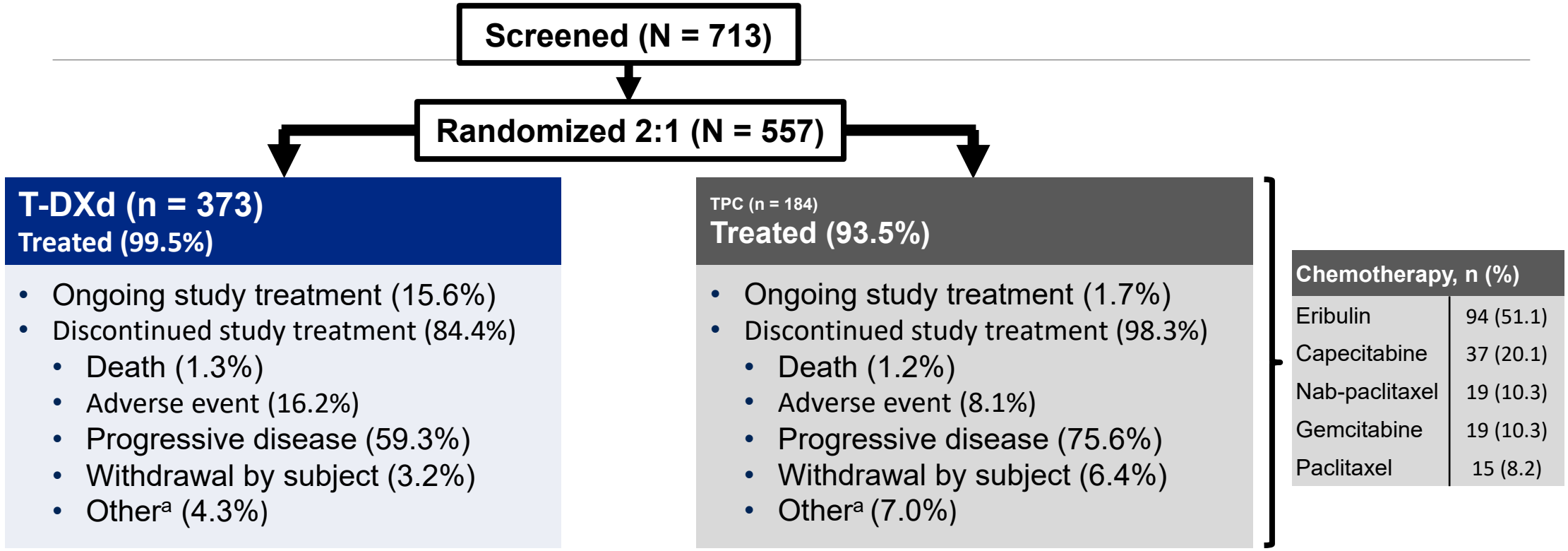
- At data cutoff (January 11, 2022), there were 321 and 370 BICR-assessed PFS events in the HR+ cohort and in all patients, respectively
- At data cutoff, 61 patients remained on treatment (58 on T-DXd and 3 on TPC), and median follow-up was 18.4 months

OS analysis

- 199 events in the HR+ cohort and 239 events in all patients
- Stopping boundary for first interim OS analysis:
  - Efficacy boundary for superiority: $P < 0.0075$

BICR, blinded independent central review; HR, hormone receptor; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Patient Disposition



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

T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Other includes clinical progression, physician decision, lost to follow-up, and other unknown reasons.

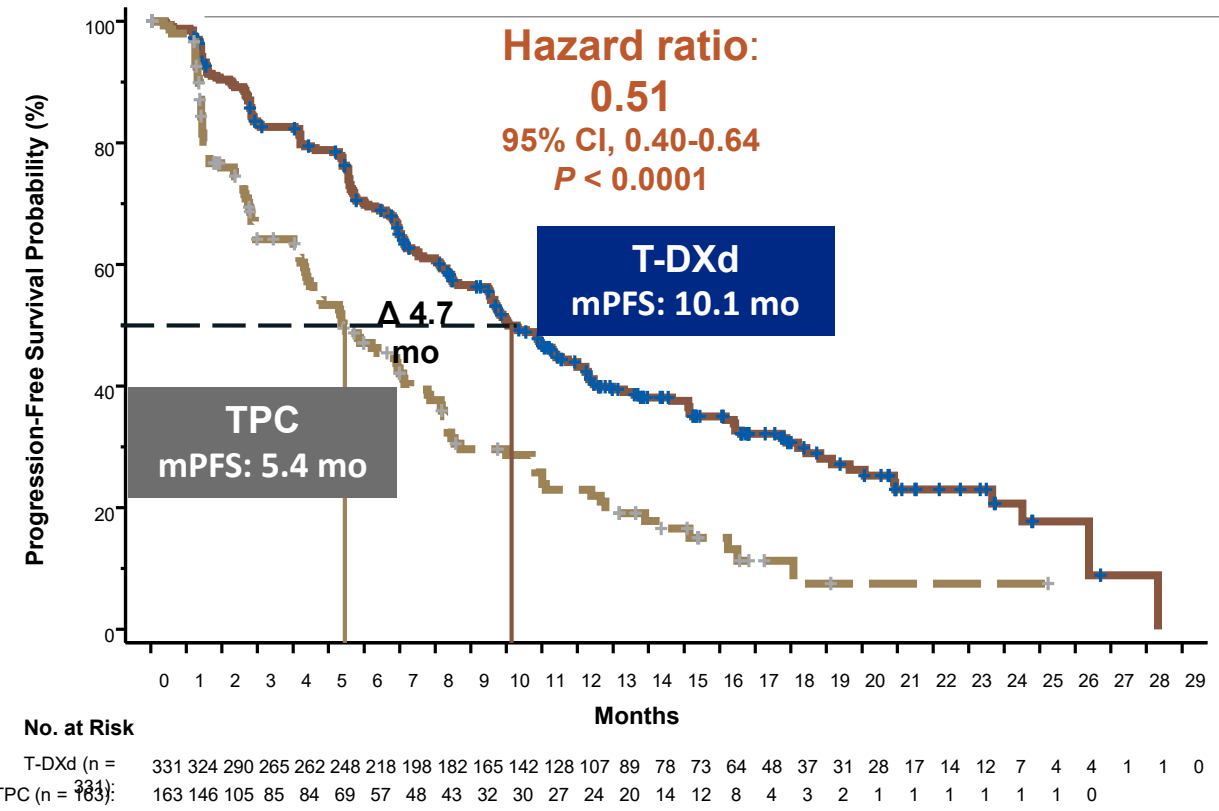
Prior Therapies

	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)

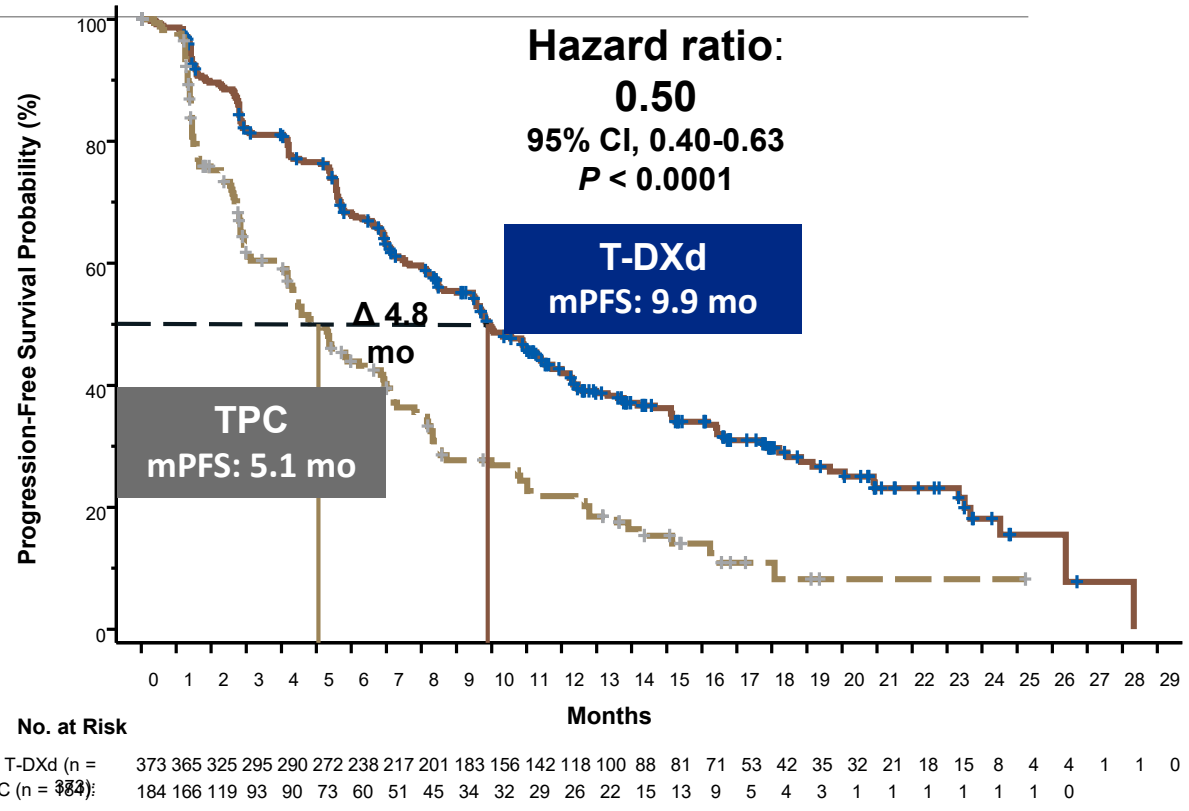
Based on derived data, which includes protocol deviations. CDK, cyclin-dependent kinase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS in HR+ and All Patients

Hormone receptor–positive



All patients

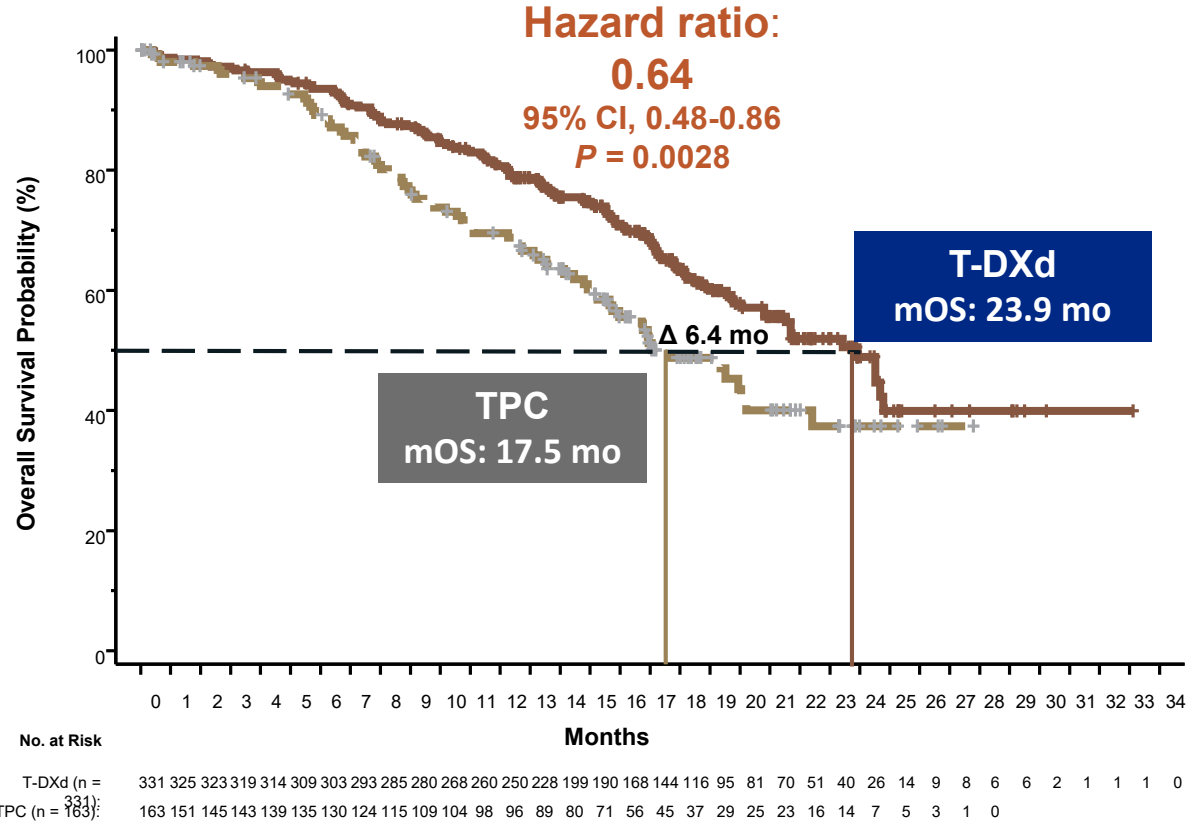


PFS by blinded independent central review.

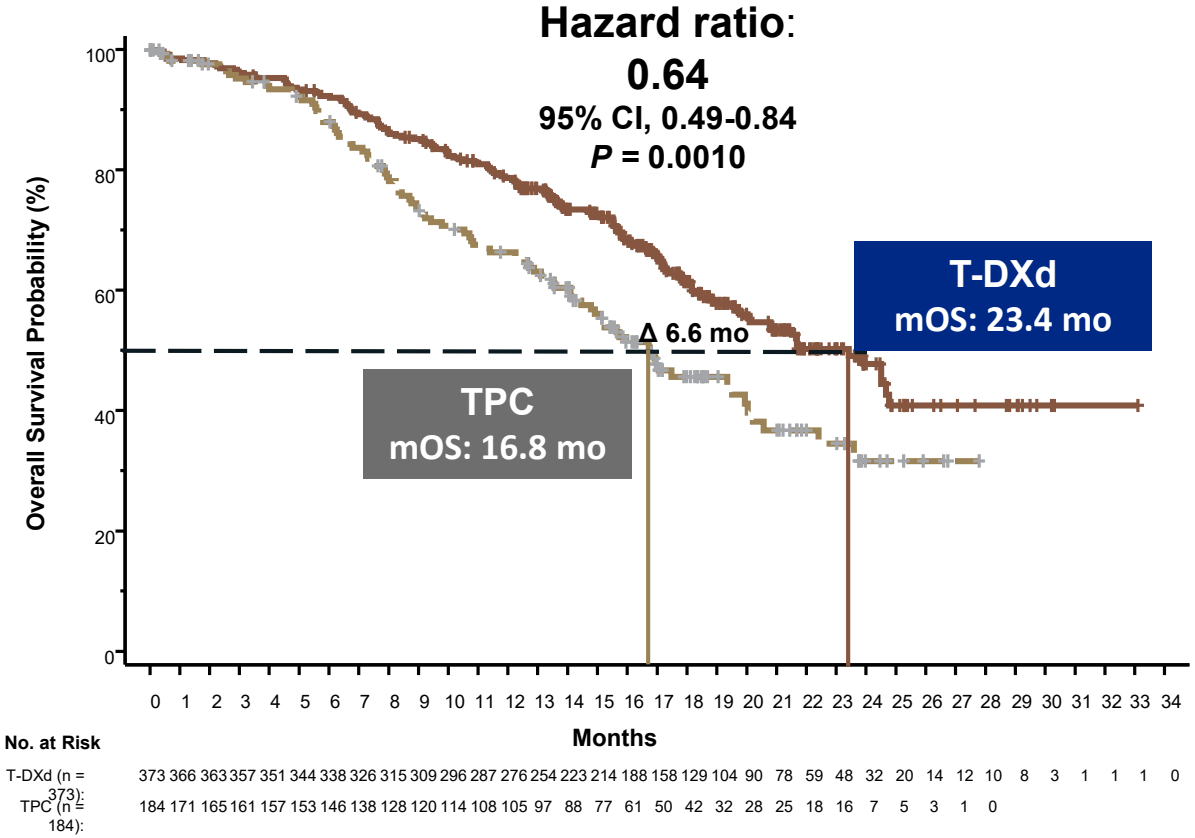
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

Hormone receptor–positive



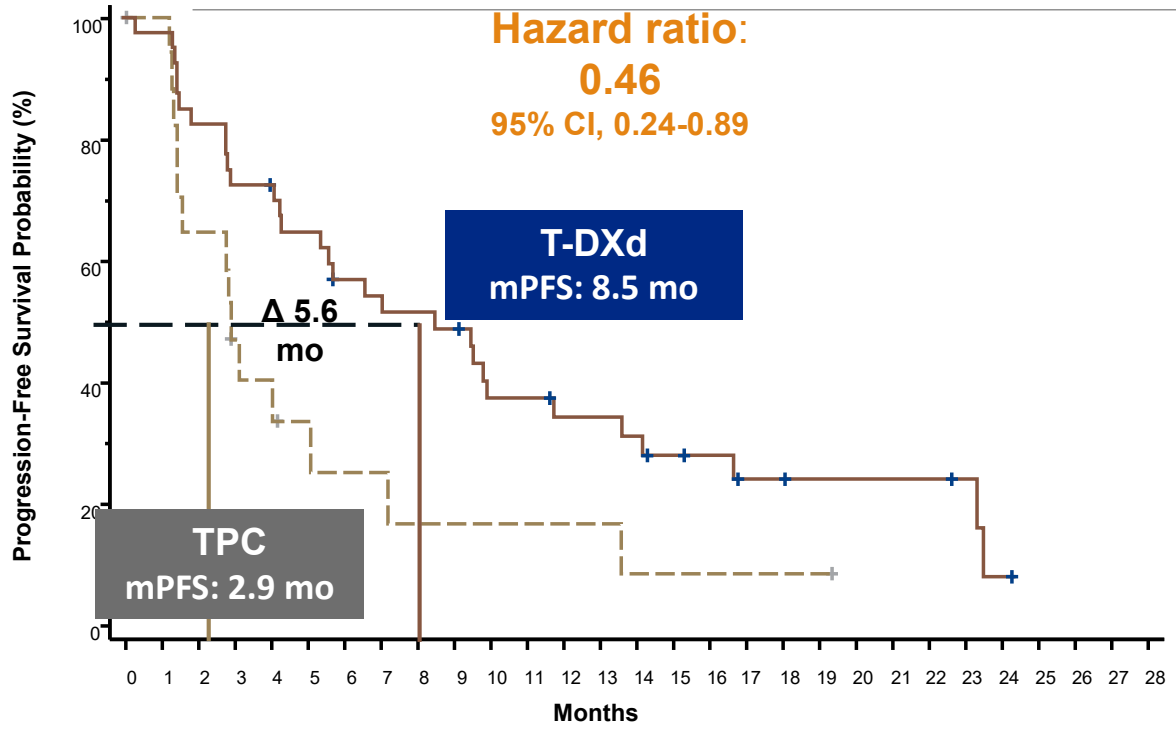
All patients



HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

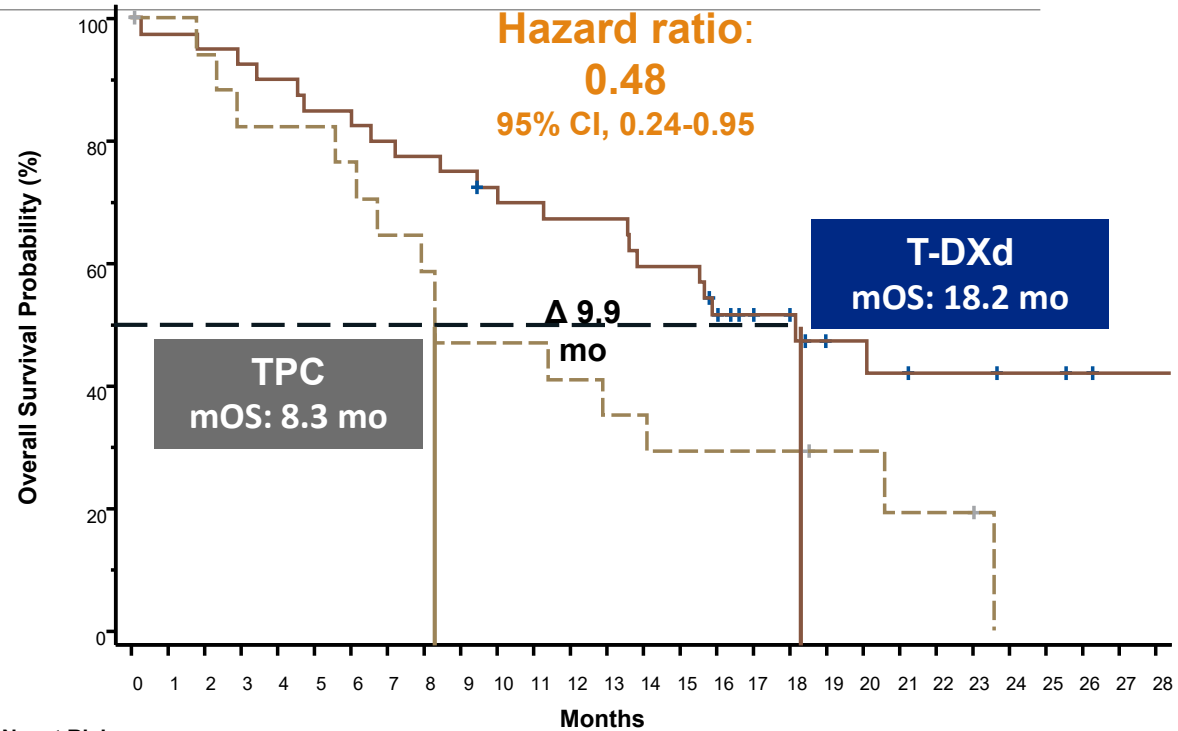
Exploratory Endpoints: PFS and OS in HR−

Hormone receptor–negative



No. at Risk

T-DXd (n = 40):	40	39	33	29	28	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	4	3	1	0	
TPC (n = 18):	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	0						



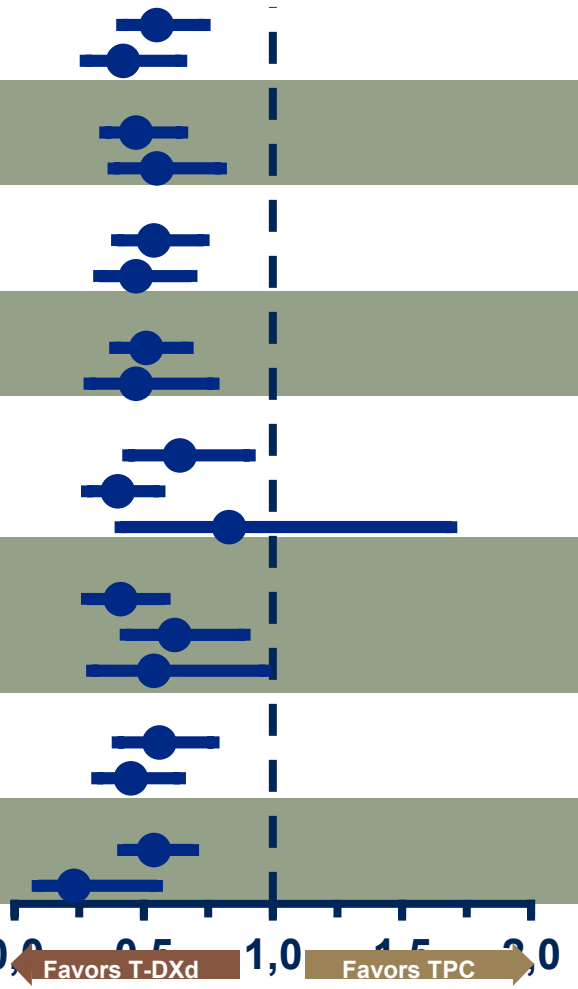
No. at Risk

T-DXd (n = 40):	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n = 18):	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

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.

Subgroup Analysis: PFS in HR+

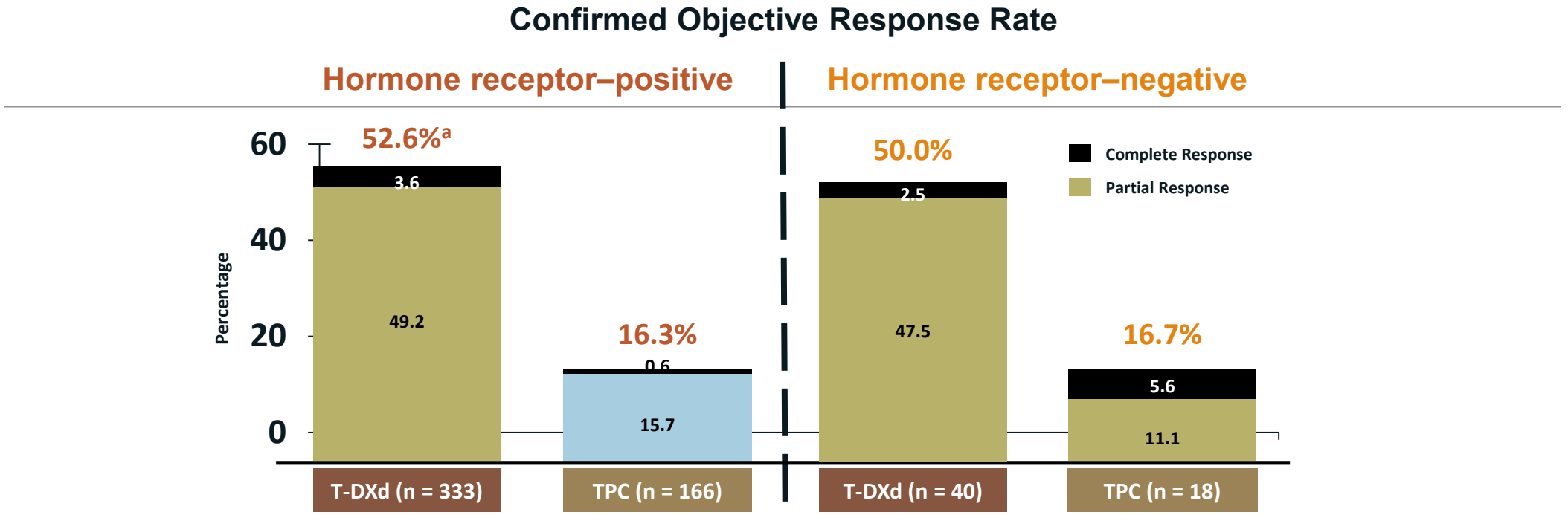
	No. of Events/No. of Patients		PFS, median (95% CI), mo		Hazard Ratio for Disease Progression or Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
IHC 2+/ISH−	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)
Prior lines of chemotherapy					
1	129/203	63/93	10.9 (8.5-12.3)	6.8 (4.5-8.2)	0.54 (0.40-0.73)
≥2	81/127	47/69	9.9 (8.3-11.7)	4.6 (2.8-6.2)	0.47 (0.33-0.68)
Age					
<65 years	170/260	79/120	9.8 (8.4-11.3)	5.4 (4.1-7.8)	0.51 (0.39-0.67)
≥65 years	41/71	31/43	12.0 (9.5-14.7)	5.6 (4.3-10.8)	0.47 (0.29-0.77)
Race					
White	100/156	43/78	10.0 (8.5-12.2)	7.1 (4.0-10.0)	0.64 (0.44-0.91)
Asian	83/131	54/66	11.0 (8.4-13.8)	4.8 (4.2-6.4)	0.40 (0.28-0.56)
Other	25/37	11/16	6.0 (5.4-10.5)	7.0 (1.4-11.0)	0.83 (0.41-1.69)
Region					
Asia	81/128	48/60	10.9 (8.4-14.7)	5.3 (4.2-6.8)	0.41 (0.28-0.58)
Europe and Israel	90/149	44/73	10.8 (8.5-13.0)	7.1 (3.0-10.7)	0.62 (0.43-0.89)
North America	40/54	18/30	8.5 (6.3-11.3)	4.5 (2.9-8.2)	0.54 (0.30-0.97)
ECOG performance status					
0	116/187	55/95	10.9 (9.5-13.0)	7.0 (4.2-8.5)	0.56 (0.40-0.77)
1	95/144	55/68	9.7 (7.3-11.5)	4.6 (2.9-6.2)	0.45 (0.32-0.64)
Visceral disease at baseline					
Yes	196/298	100/146	9.8 (8.5-11.1)	5.8 (4.4-7.1)	0.54 (0.42-0.69)
No	15/33	10/17	17.9 (10.9-26.4)	4.5 (1.6-12.4)	0.23 (0.09-0.55)



PFS by blinded independent central review. Based on derived data, which include protocol deviations.

CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

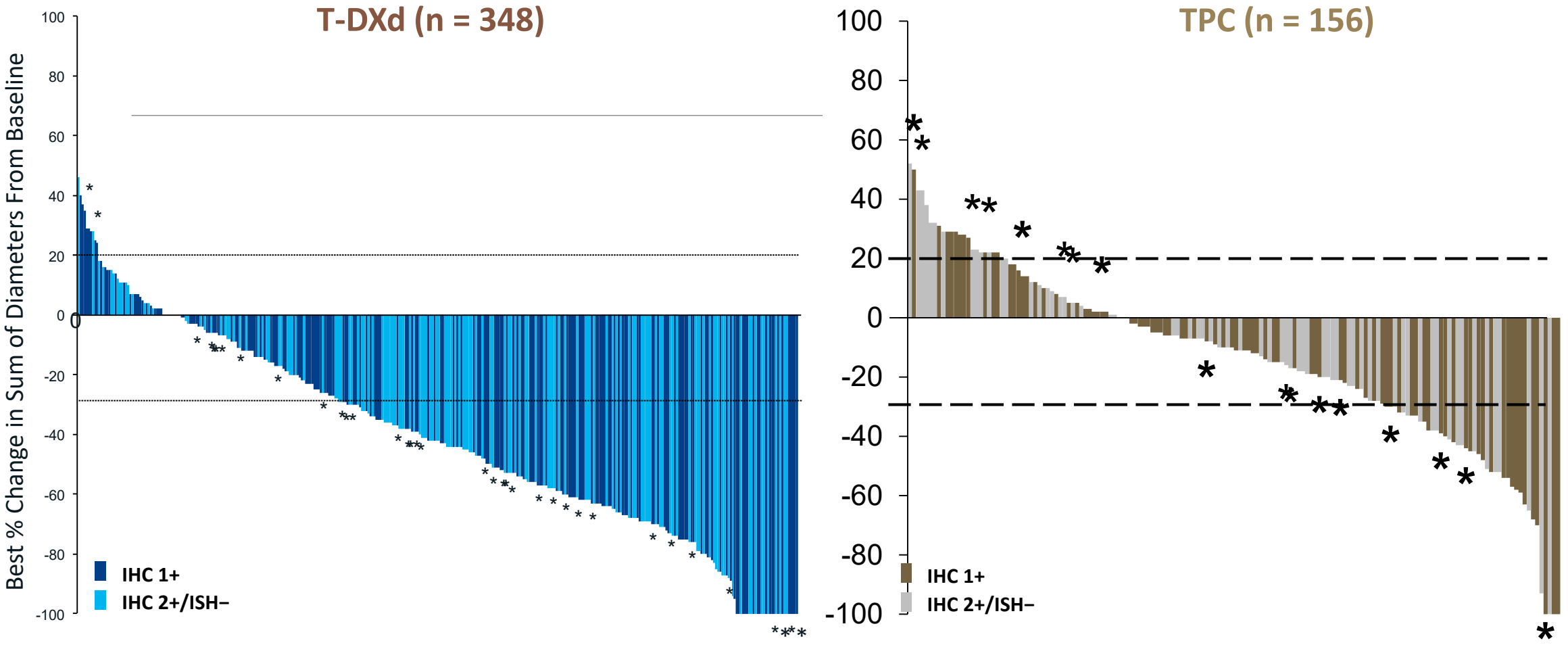
Confirmed ORR



	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.

Best Change in Target Lesions (All Patients)



*Patients with HR− disease

Shown are the best percentage changes from baseline in the sum of the largest diameters of measurable tumors in patients for whom data from both baseline and postbaseline assessments of target lesions by independent central review were available. The upper dashed horizontal line indicates a 20% increase in tumor size in the patients who had disease progression, and the lower dashed line indicates a 30% decrease in tumor size (partial response).

HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

So what is HER2 low breast cancer in the clinic?

- Approximately 45–55% of Breast Cancer using variable HER2 scoring criteria prior to the T-DXd trial
- Since the introduction of “HER2-low” in 2020, a few studies have reported the incidence of HER2-low BC as between 31% and 51%
  - It is more common in HR+ positive BCs (ranges: 43.5–67.6%) than TNBCs (ranges:15.7–53.6%)
  - More specifically, in the advanced BCs, the reported incidence of HER2-low BC ranged from 35.2–63.2%
- Seem to be more like ER+ve cancer
  - Mostly Luminal A (29.3–65.5%); Luminal B: 22.8–50.5%; Basal: 4.6–7.7%; HER2-enriched: 1.1–4.1%;
  - Tend to have a lower Ki-67 proliferation index
  - Less responsive to neoadjuvant chemotherapy (NAC) with a pCR rate between 9.8% and 36.3%
- Some evidence for instability in the level of HER2 in HER2 low (Tarantino EJC 2022)
- Denkert et al (2021) analysed patients in NeoSACT trials (so not representative of the full spectrum of breast cancer) with non HER2 amplified cancers
  - 50% of non HER2 amplified cases
  - 2/3 were ER+ve
  - Lower pCR rate in ER+ve cases ONLY
  - Better survival in ER negative cases

Does the level of ER matter in HER2-low cancers?

- HER2-low, ER-low (IHC 1-10%) breast cancers tend to mimic TNBC, which accounts for 10-15% of breast cancers[1,2]

- ASCO/CAP guidelines recommend an IHC ER expression cutoff of ≥1% for ER positive tumors, however, endocrine therapy studies are increasingly using a higher cut-off of 10%[2,3]
- Potential for 3 classifications of ER expression: negative (IHC 0%), low (IHC 1-10%), and positive (IHC >10%)
- This subgroup analysis explored efficacy and safety outcomes for T-DXd versus TPC in the subset of patients from the DESTINY-Breast04 study[4] with low ER expression (IHC 1-10%)

Baseline Demographic Characteristics of ER Subgroups

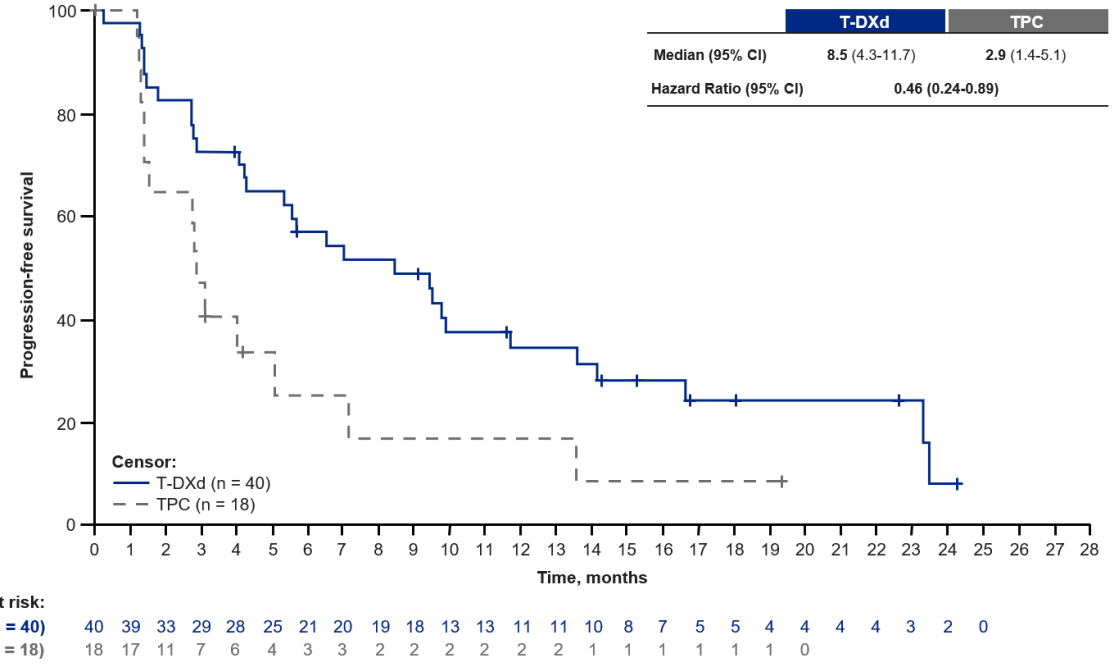
	ER-negative (IHC 0%)		ER-low (IHC 1-10%)	
Baseline Characteristic[a]	**T-DXd (n = 40)**	**TPC (n = 18)**	**T-DXd (n = 35)**	**TPC (n = 17)**
Age				
Median (range), years	58.9 (36.6-78.9)	55.9 (32.6-80.5)	57.6 (31.5-76.4)	50.6 (32.6-69.7)
Age < 65 years, n, (%)	30 (75.0)	13 (72.2)	31 (88.6)	16 (94.1)
Age ≥ 65 years, n, (%)	10 (25.0)	5 (27.8)	4 (11.4)	1 (5.9)
Race, n (%)				
White	19 (47.5)	11 (61.1)	15 (42.9)	10 (58.8)
Black or African American	0	1 (5.6)	1 (2.9)	1 (5.9)
Asian	20 (50.0)	6 (33.3)	14 (40.0)	5 (29.4)
Other	1 (2.5)	0	5 (14.3)	1 (5.9)
Previous CDK4/6i, n (%)				
Yes	2 (5.0)	0	22 (62.9)	9 (52.9)
No	38 (95.0)	18 (100)	12 (34.3)	8 (47.1)
Missing	0	0	1 (2.9)	0
Number of prior lines of chemotherapy, n (%)				
1	16 (40.0)	5 (27.8)	21 (60.0)	8 (47.1)
2	24 (60.0)	13 (72.2)	14 (40.0)	9 (52.9)
HER2 IHC/ISH status, n (%)				
HER2 1+	22 (55.0)	10 (55.6)	17 (48.6)	12 (70.6)
HER2 2+/ISH-	18 (45.0)	8 (44.4)	18 (51.4)	5 (29.4)
PR expression, n (%)[b]				
PR staining 1-10% of cells positive	0	0	20 (57.1)	4 (23.5)
PR staining > 10% of cells positive	0	0	4 (11.4)	3 (17.6)
PR staining unknown	0	0	0	0
Negative	40 (100.0)	18 (100.0)	11 (31.4)	10 (58.8)
Baseline liver metastases, n (%)	19 (47.5)	5 (27.8)	23 (65.7)	8 (47.1)
Baseline CNS metastases, n (%)	5 (12.5)	1 (5.6)	1 (2.9)	2 (11.8)
Pretreated anthracycline status, n (%)	30 (75.0)	9 (50.0)	25 (71.4)	12 (70.6)

CNS, central nervous system; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PR, progesterone receptor; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]All patients (100%) in each subgroup were female. [b]No patients in either subgroup had indeterminate PR expression.

PFS in Patients by ER Expression

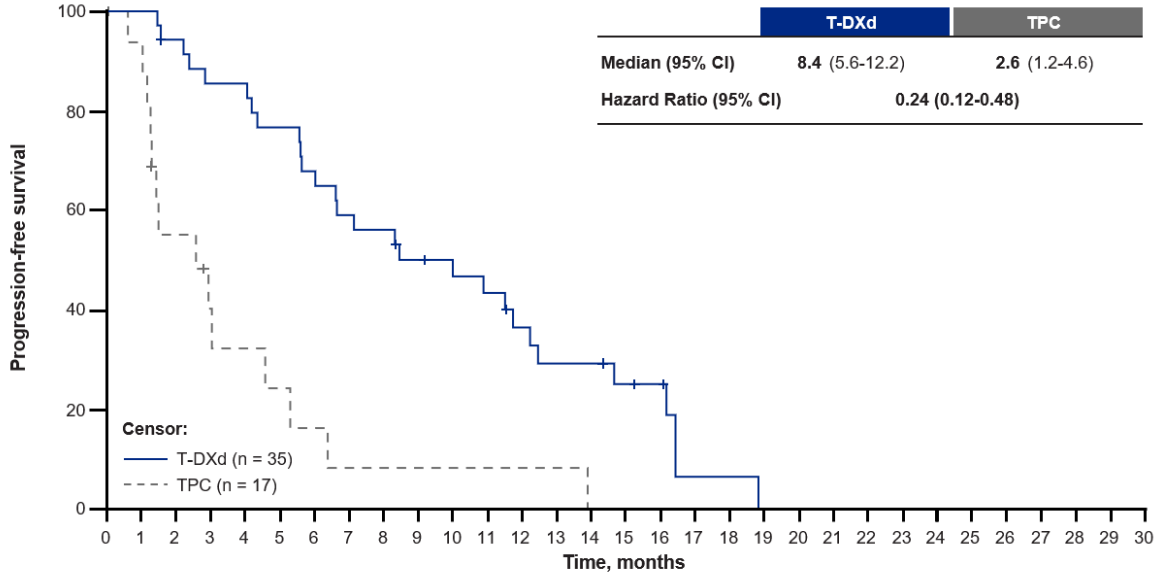
Patients with ER-negative (IHC 0%)



No. at risk:

T-DXd (n = 40)	40	39	33	29	28	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	3	2	0
TPC (n = 18)	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	0				

Patients with ER-low (IHC 1-10%)



No. at risk:

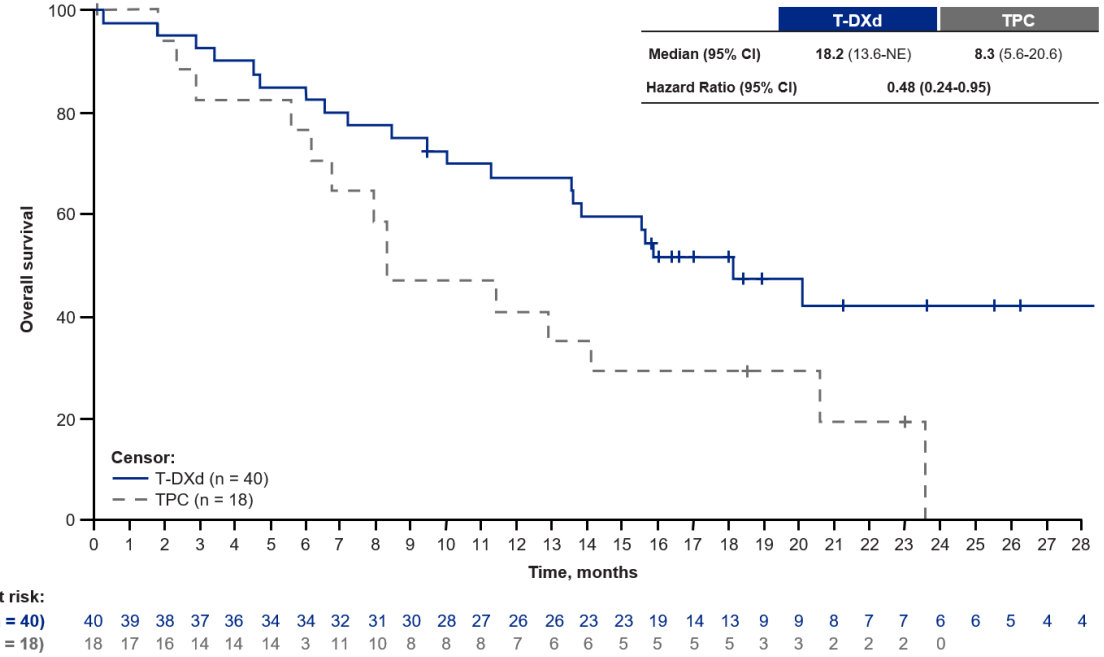
T-DXd (n = 35)	35	35	32	29	29	26	23	20	19	16	14	13	10	8	8	6	5	1	1	0					
TPC (n = 17)	17	15	8	4	4	3	2	1	1	1	1	1	1	1	0										

- T-DXd achieved better PFS outcomes compared with TPC

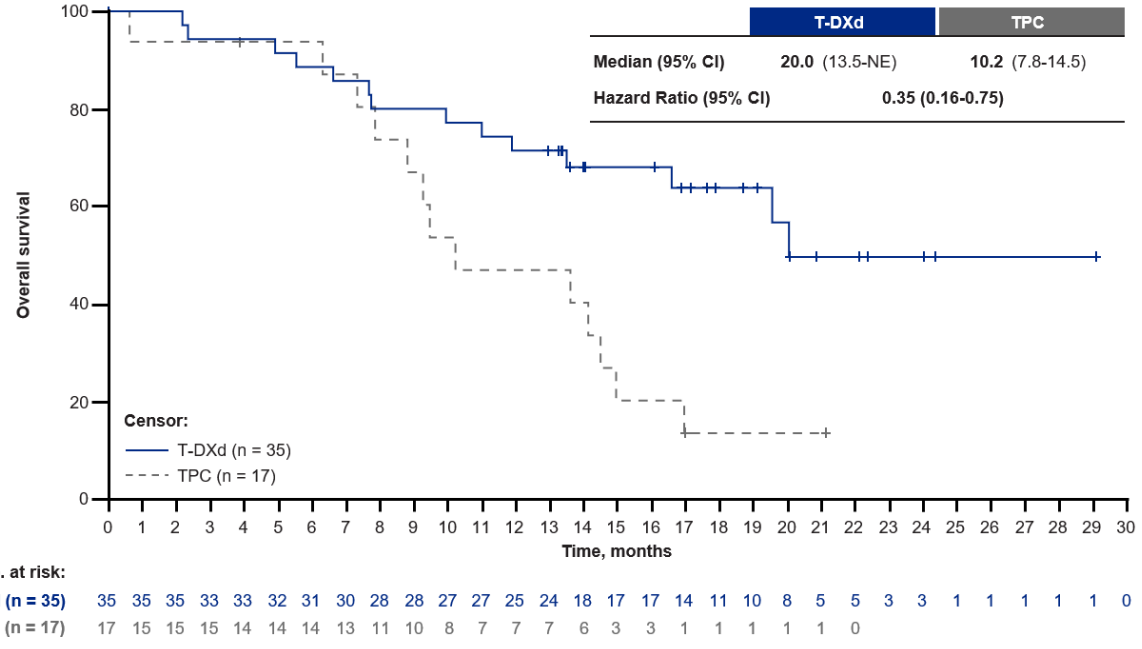
CI, confidence interval; ER, estrogen receptor; IHC, immunohistochemistry; NE, not estimable; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Cutoff date: January 11, 2022.
[a]Analysis conducted in the full analysis set.

OS in Patients by ER Expression

Patients with ER-negative (IHC 0%)



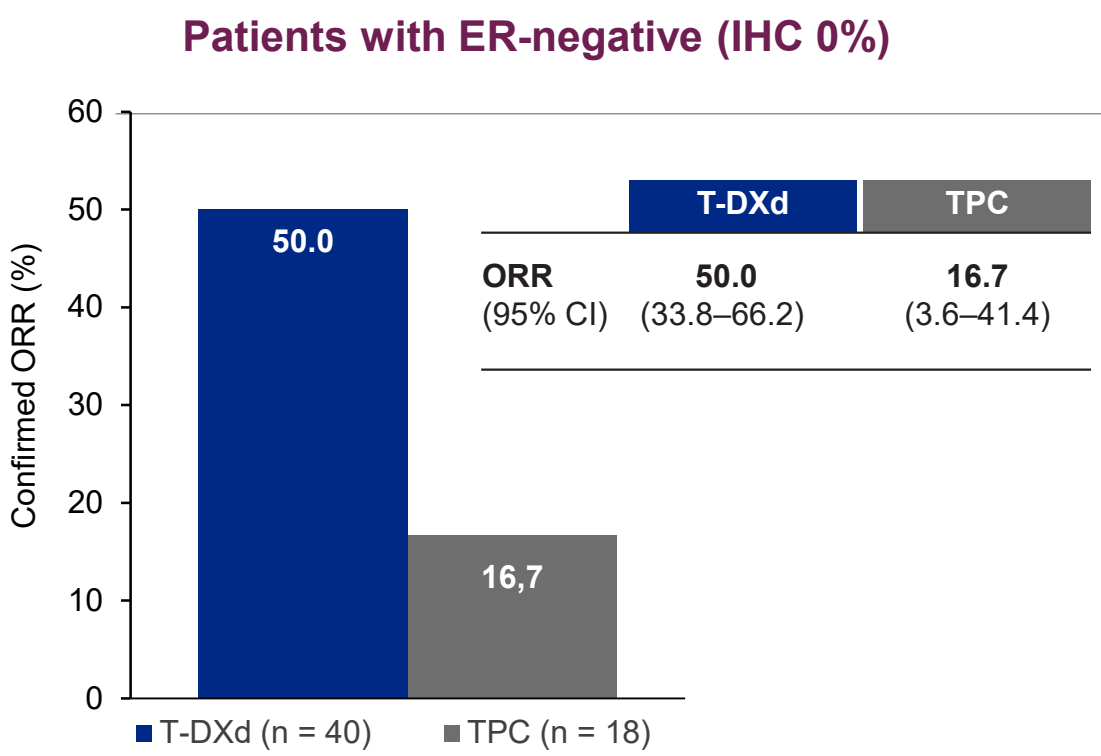
Patients with ER-low (IHC 1-10%)

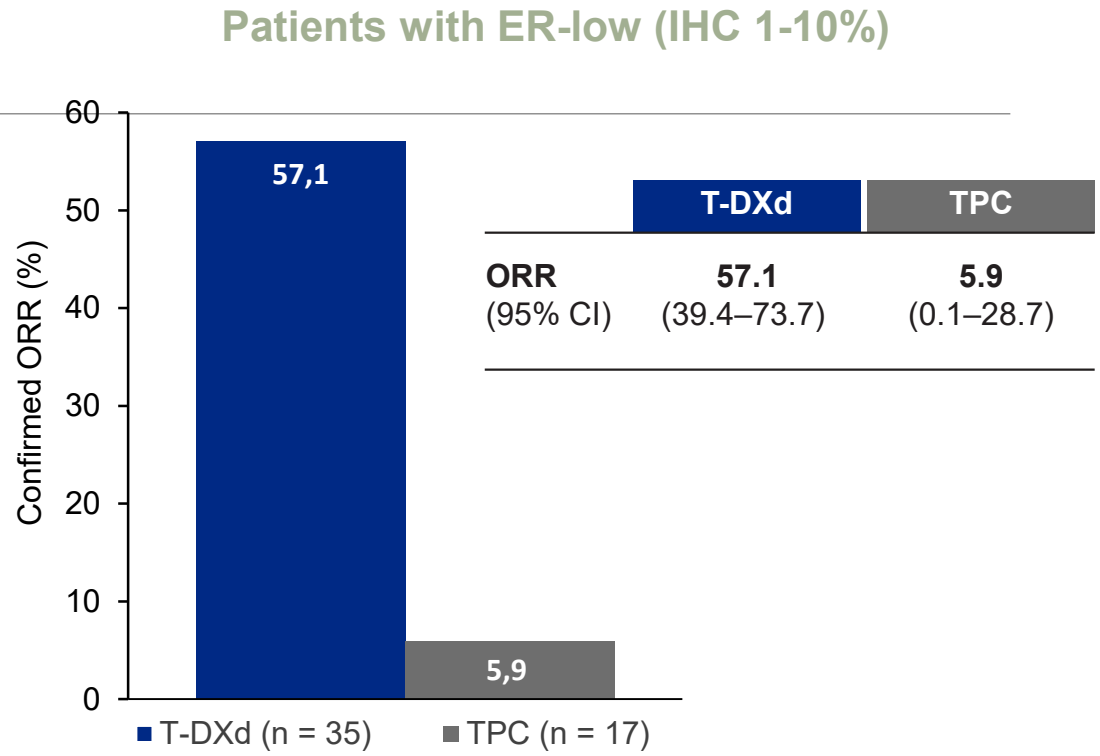


- T-DXd achieved better OS outcomes compared with TPC

CI, confidence interval; ER, estrogen receptor; IHC, immunohistochemistry; NE, not estimable; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Cutoff date: January 11, 2022.
[a]Analysis conducted in the full analysis set.

ORR in Patients by ER Expression





- Confirmed ORR is higher with T-DXd versus TPC, regardless of ER expression

ER, estrogen receptor; IHC, immunohistochemistry; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Reported as hormone receptor-negative cohort in Modi S et al.
Modi S et al. *N Engl J Med*. 2022;387(1):9-20.

DAISY: Study Design

- *A multicenter, open-label, phase 2 trial (NCT04132960)*

- Patients with mBC*
- ≥ 18 years old
- ≥ 1 chemotherapy regimen in metastatic setting

COHORT 1 HER2 overexpressing: HER2 IHC 3+ or IHC 2+/ISH+ (*n*=72)
- Previous taxanes
- Resistant to trastuzumab and TDM-1

COHORT 2 HER2-low: HER2 IHC 2+/ISH- or IHC 1+ (*n*=74)
- Previous anthracyclines and taxanes
- If HR+: resistant to CDK4/6 inhibitors plus HT

COHORT 3 HER2 non-expressing: HER2 IHC 0 (*n*=40)
- Previous anthracyclines and taxanes
- If HR+: resistant to CDK4/6 inhibitors plus HT

T-DXd IV 5,4 mg/kg Q3W
Upon PD or unacceptable toxicity

OBJECTIVES

- ***PRIMARY***

BOR rate in each cohort by investigator assessment

- ***SECONDARY***
  - **EFFICACY**

BOR rate in each cohort by central review
PFS
OS
DOR
CBR

  - **SAFETY**

- ***EXPLORATORY***

Translational research

*Patients enrolled from November 2019-March 2021. HR+: hormone receptor-positive; CDK4/6: cyclin-dependent kinase 4/6; HT: hormone therapy; BOR: best objective response; OS: overall survival; DOR: duration of response; CBR: clinical benefit rate; IV: intravenously; Q3W: every 3 weeks; PD: progressive disease

DAISY: Patients Characteristics

	TOTAL n=179	COHORT 1 HER2 IHC 3+ or IHC 2+/ISH+ n=68	COHORT 2 HER2 IHC 2+/ISH- or IHC 1+ n=73	COHORT 3 HER2-IHC0 n=38
HER2 status review				
IHC0+ (≤ 10% HER2 cells)	38 (21.2%)	0	0	38 (100%)
IHC1+	41 (22.9%)	0	41 (56.2%)	0
IHC2+/ISH-	32 (17.9%)	0	32 (43.8%)	0
IHC2+/ISH+	17 (9.5%)	17 (25.0%)	0	0
IHC3+	50 (27.9%)	50 (73.5%)	0	0
IHC1+/ISH+	1 (0.6%)	1 (1.5%)	0	0
Primary tumor – HR status				
HR-	51 (28.5%)	24 (35.3%)	15 (20.5%)	12 (31.6%)
HR+	128 (71.5%)	44 (64.7%)	58 (79.5%)	26 (68.4%)
WHO PS				
0	77 (43.0%)	21 (30.9%)	33 (45.2%)	23 (60.5%)
1	102 (57.0%)	47 (69.1%)	40 (54.8%)	15 (39.5%)
Number of previous lines of metastatic treatment				
0 line	1 (0.6%)	0	1 (1.4%)	0
1 line	12 (6.7%)	2 (2.9%)	5 (6.8%)	5 (13.2%)
2 lines	19 (10.6%)	10 (14.7%)	6 (8.2%)	3 (7.9%)
3 lines	22 (12.3%)	9 (13.2%)	9 (12.3%)	4 (10.5%)
4 lines	30 (16.8%)	11 (16.2%)	14 (19.2%)	5 (13.2%)
5 lines	27 (15.1%)	9 (13.2%)	8 (11.0%)	10 (26.3%)
6 lines and more	68 (38.0%)	27 (39.7%)	30 (41.1%)	11 (28.9%)

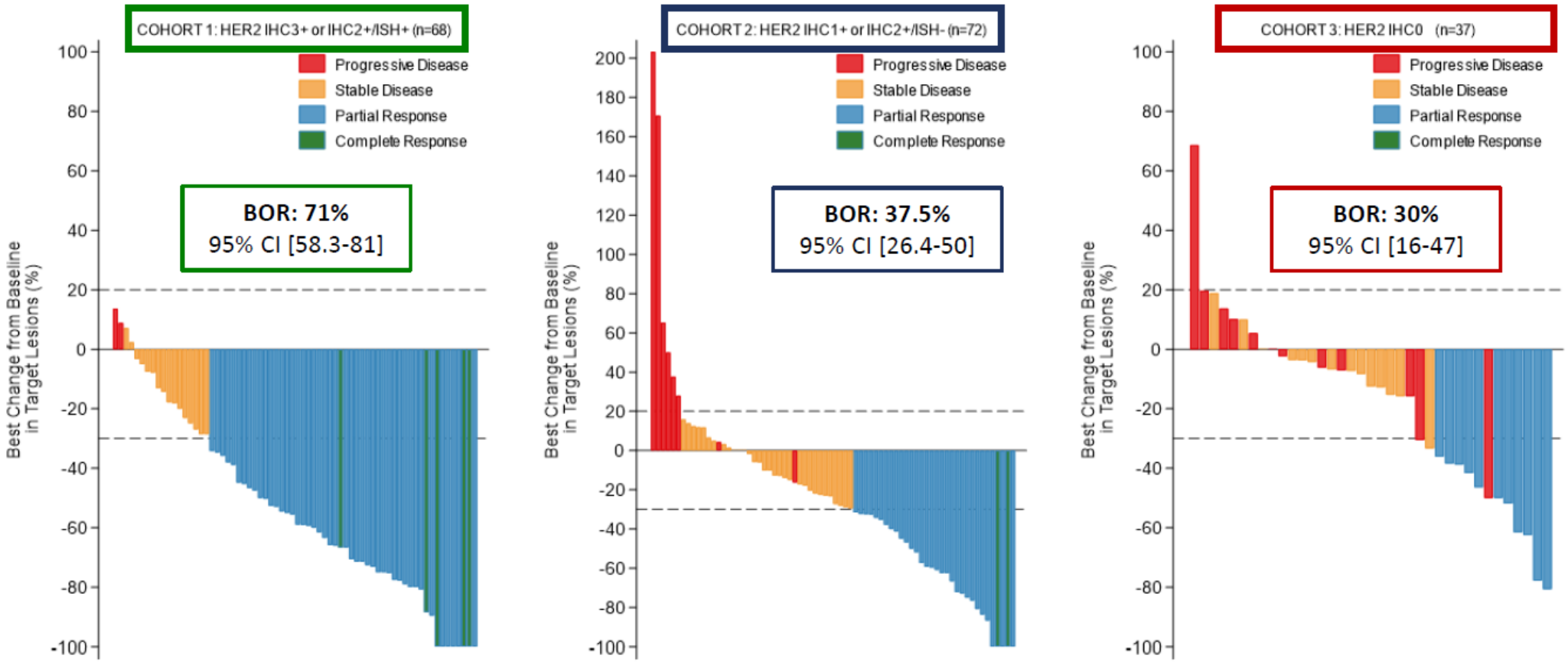
Data cut-off: Oct 19, 2021

Dieras et al, Abstract PD8-02 SABCS 2021

Investigator-reported T-DXd activity in the 3 cohorts at a median follow-up of 15.6 months

	Total	Cohort 1 (HER2 over-expressing)	Cohort 2 (HER2 low-expressing)	Cohort 3 (HER2 non-detected)
BOR confirmed n / N [95%CI]	86 / 177 (48.6%) [41.0; 56.2]	48 / 68 (70.6%) [58.3; 81.0]	27 / 72 (37.5%) [26.4; 49.7]	11 / 37 (29.7%) [15.9; 47.0]
Median DOR (months) [95%CI]	8.5 [6.5; 9.8]	9.7 [6.8; 13]	7.6 [4.2; 9.2]	6.8 [2.8; Not reached]
Median PFS (months) [95%CI]	7.0 [6.0; 8.7]	11.1 [8.5; 14.4]	6.7 [4.4; 8.3]	4.2 [2.0; 5.7]

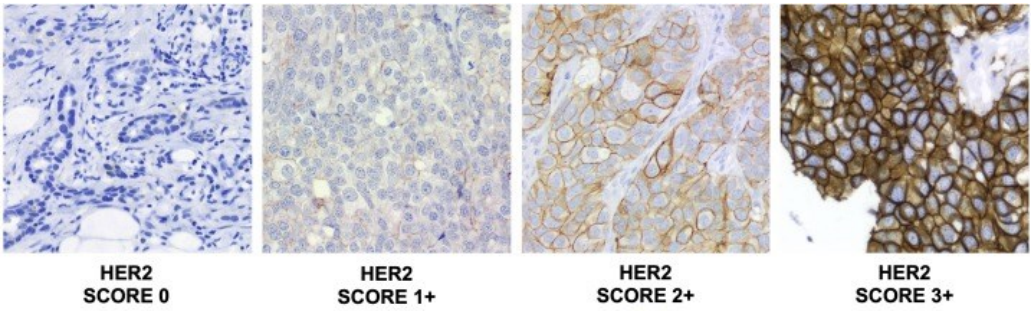
DAISY: BOR rate according to HER2 expression

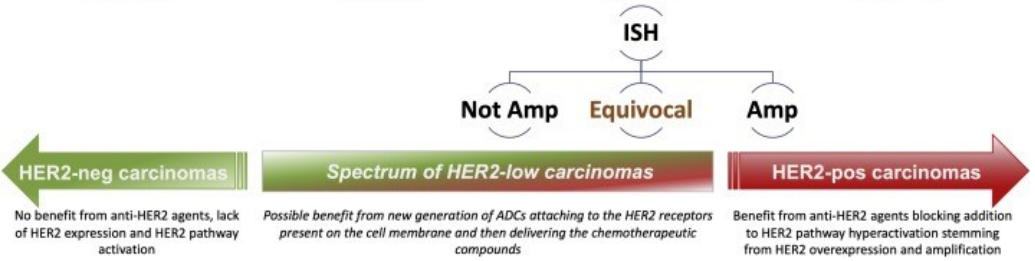


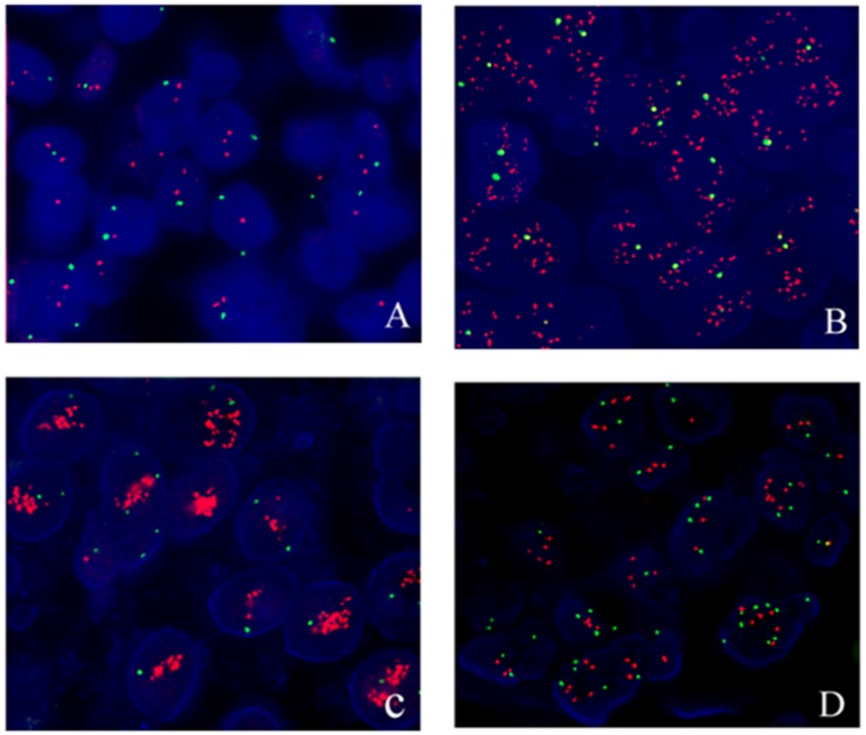
THE BOR RATE IS DEFFERENT BETWEEN THE THREE COHORTS p <0.0001

Data cut-off: Oct 19, 2021

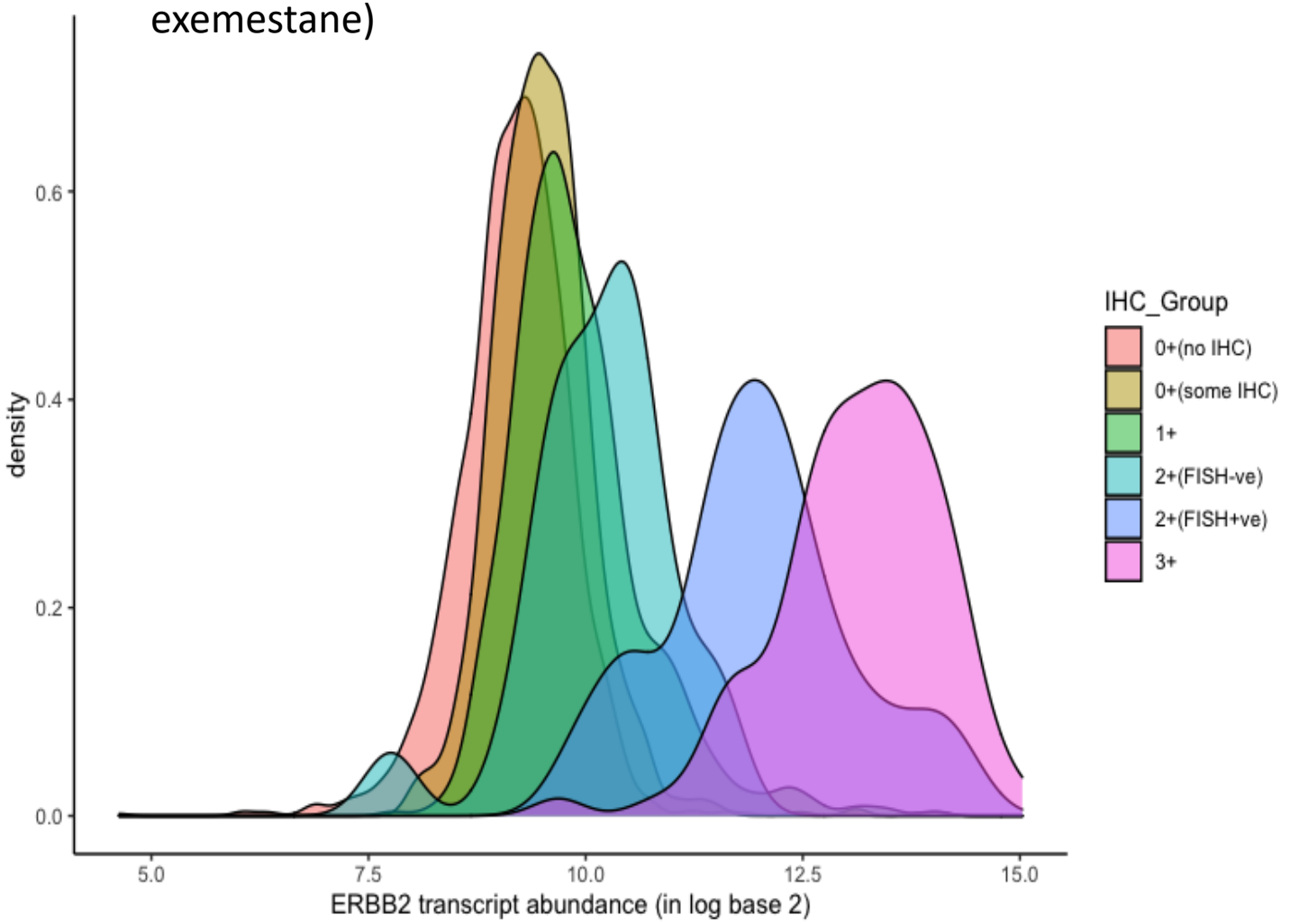
NCT04132960







Data from the TEAM trial (luminal cancers, tamoxifen vs exemestane)



What is the cut-off to identify cancers that DONT respond to T-DXd ?

Minimal differences between HER2 low (1+/2+) and HER2 (0)

	HER2-low (n=192)	HER2-zero (n=140)
Age, years (SD)	57 (14)	58 (14)
PAM50 subtype, n (%)		
Luminal A	114 (60.0)	78 (55.7)
Luminal B	73 (38.4)	59 (42.1)
HER2-enriched	2 (1.0)	2 (1.4)
Basal-like	1 (0.6)	1 (0.8)
Risk group, n (%)		
Low	56 (29.5)	37 (26.4)
Intermediate	62 (32.6)	55 (39.3)
High	72 (37.9)	48 (34.3)
ROR score, mean (SD)	44 (21)	45 (19)
Ki67, n (%)		
Low (<20%)	96 (51.0)	59 (42.5)
High (≥20%)	92 (49.0)	80 (57.5)
PR, n (%)		
<20%	59 (30.7)	30 (21.6)
≥20%	133 (69.3)	109 (78.4)

	HER2-low (n=192)	HER2-zero (n=140)
Histology, n (%)		
Ductal	144 (75.8)	108 (77.1)
Lobular	40 (21.0)	25 (17.9)
Others	6 (3.2)	7 (5.0)
Histological Grade, n (%)		
Low/1	32 (17.0)	24 (17.4)
Intermediate/2	116 (61.7)	84 (60.9)
High/3	40 (21.3)	30 (21.7)
T stage, n (%)		
T1	109 (56.8)	82 (58.6)
T2	77 (40.1)	52 (37.1)
T3	6 (3.1)	6 (4.3)
N stage, n (%)		
N0	113 (58.9)	83 (59.3)
Nmic	29 (15.1)	21 (15.0)
N+	50 (26.0)	36 (25.7)
Menopausal status, n (%)		
Premenopausal	56 (29.5)	43 (31.8)
Postmenopausal	135 (70.5)	96 (68.2)

Table 1. Main clinical and pathological characteristics of the patients included in the analysis. SD: standard deviation. PR: progesterone

Sanchez-Bayona et al, Poster 49-P ESMO 2022:

New classification of Breast Cancer?

ER/HER2	ER negative (< 1%)	ER low (1 < < 10%)	ER positive (> 10%)
HER2 negative (?definition)	Chemo & Saci	Chemo & Saci ?ET ? Saci	Chemo & ET & Saci
HER2 Low/non amplified	T-DXd & Chemo/Saci	T-DXd & Chemo & ? ET	T-DXd & Chemo & ET
HER2 +ve (+++ or ISH+ve)	Anti-HER2 drugs/ Chemo	Anti-HER2 drugs/Chemo/ (? ET)	Anti-HER2 drugs & Chemo & ET

And for which other treatment decision does this matter…and what new targets will impact on this approach….

Conclusions

low levels of HER2 seem to predict for benefit from an antibody drug conjugate directed at HER2.

Level of ER seems irrelevant in that therapeutic approach

DAISY suggests activity even in HER2 ICH 0 cancers

- BUT some of them still have SOME expression of HER2….

How much HER2 needs to be expressed for the drug to work?

Sacituzumab-govitecan works without worrying about the level of the target (TROP2), in both ER negative and ER positive breast cancers…..

Do we just need a minimum level of cell-surface target to get the drug into the cell?