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POLICLINICO DI SANT'ORSOLA

ADC nel carcinoma mammario HER2+ e HER2 low

Claudio Zamagni
Direttore Oncologia Medica senologica e ginecologica & Breast Unit
IRCCS Azienda Ospedaliero-universitaria di Bologna
Ospedale di Sant'Orsola

Studies of the HER-2/*neu* Proto-oncogene in Human Breast and Ovarian Cancer

DENNIS J. SLAMON,* WILLIAM GODOLPHIN, LOVELL A. JONES, JOHN A. HOLT, STEVEN G. WONG, DUANE E. KEITH, WENDY J. LEVIN, SUSAN G. STUART, JUDY UDOVE, AXEL ULLRICH, MICHAEL F. PRESS

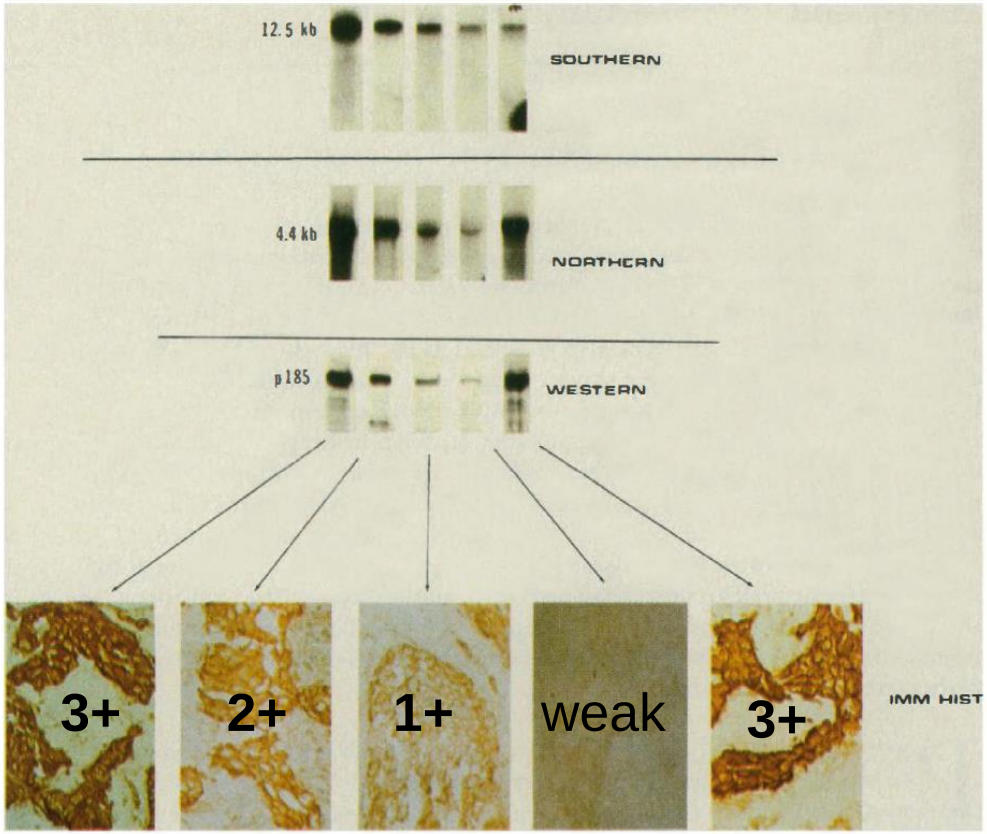


Fig. 1. Examples of the correlation between HER-2/*neu* gene amplification and expression. Southern

Table 1. Univariate and multivariate survival analyses comparing disease-free (relapse) and overall survival to prognostic factors in 345 node-positive breast cancer patients. Statistical analyses were performed by the χ^2 test and by Cox's partially nonparametric regression analysis to evaluate the predictive power of various combinations and interactions of prognostic factors in a multivariate manner as described (*5*). Prognostic parameters evaluated include number of nodes (Nodes), HER-2/*neu* gene amplification (HER-2/*neu*), estrogen receptor (ER), progesterone receptor (PGR), size of primary tumor (Size), and age of patient at diagnosis (Age). The median follow up was 57 months (60 months for those still alive).

	Disease free survival		Overall survival	
	Univariate (*P*)	Multivariate (*P*)*	Univariate (*P*)	Multivariate (*P*)*
Nodes	<0.0001	<0.0001 [0.0818 ± 0.0214]	<0.0001	<0.0001 [0.0912 ± 0.0346]
HER-2/*neu*	0.01	0.006 [0.1142 ± 0.0413]	0.041	0.045 [0.0864 ± 0.0288]
ER	0.235	0.60	0.091	0.157
PGR	0.045	0.07	0.20	0.24
Size	0.003	0.15	0.006	0.16
Age	0.92	0.96	0.20	0.11

*Regression coefficients ± SE are shown in square brackets.

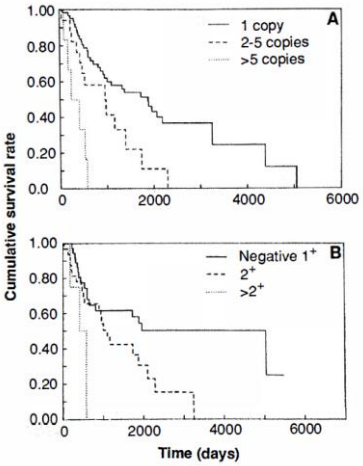
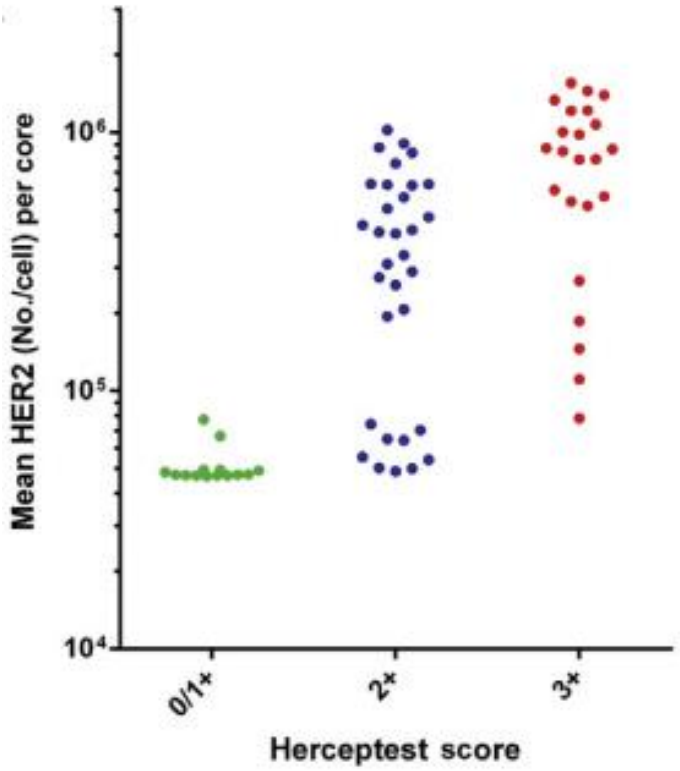
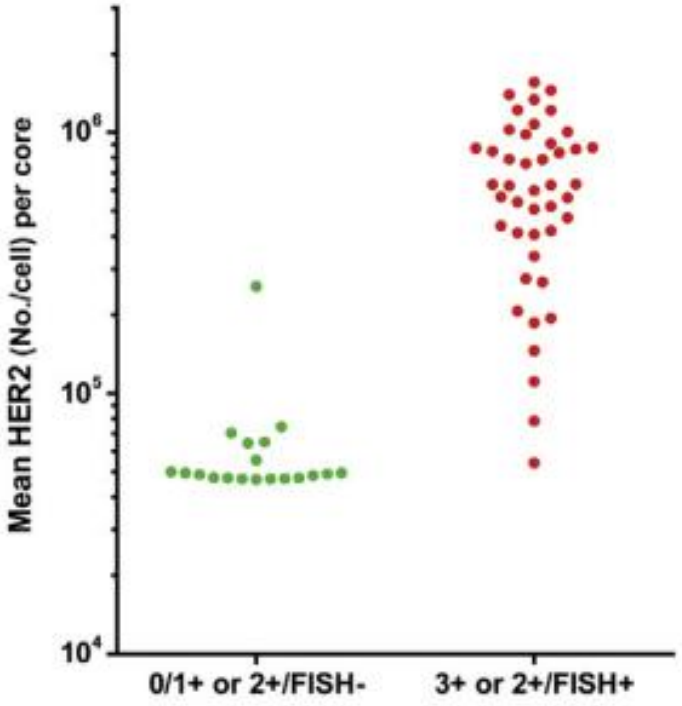


Fig. 4. Actuarial survival curves for patients with ovarian cancer evaluating (**A**) the association of HER-2/*neu* gene amplification with survival and (**B**) the association of HER-2/*neu* expression as determined by histochemical analyses and survival. The *P* values for these two curves are <0.0001 and 0.0126, respectively. The Kaplan-Meier

Science May 12, 1989

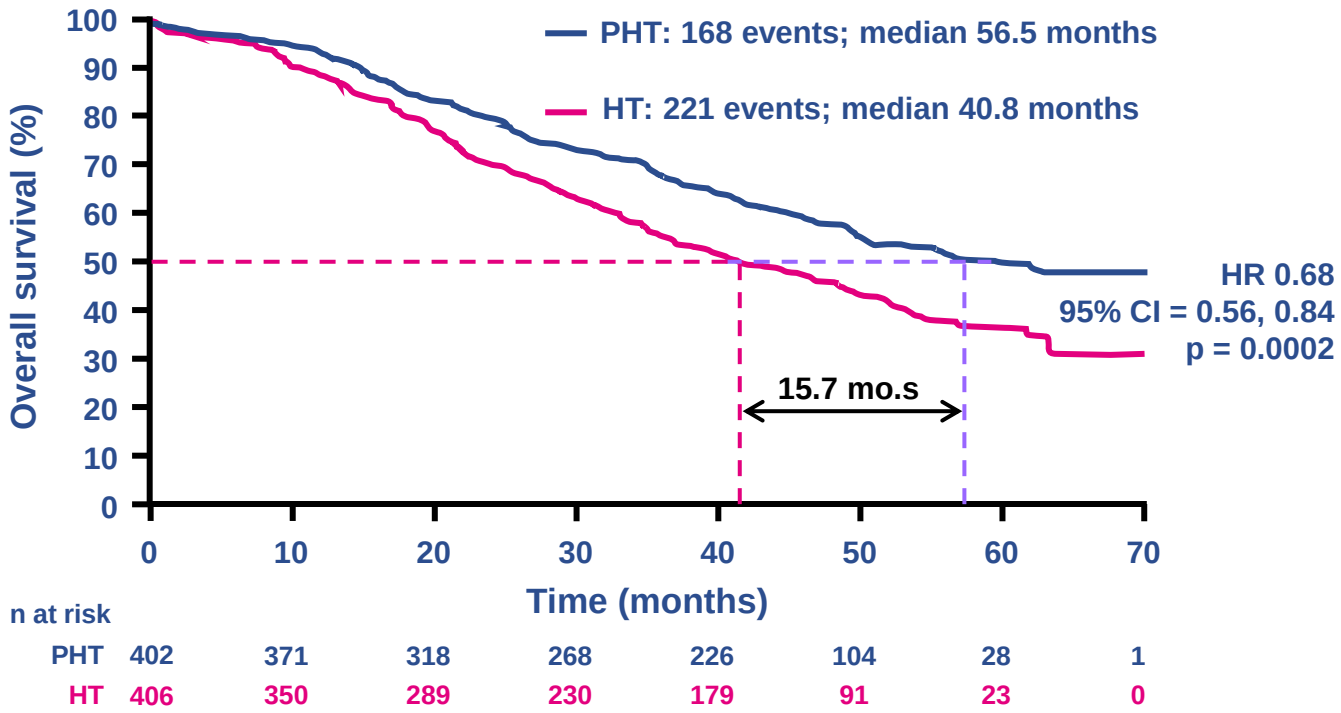
Single-Cell Quantitative HER2 Measurement Identifies Heterogeneity and Distinct Subgroups within Traditionally Defined HER2-Positive Patients





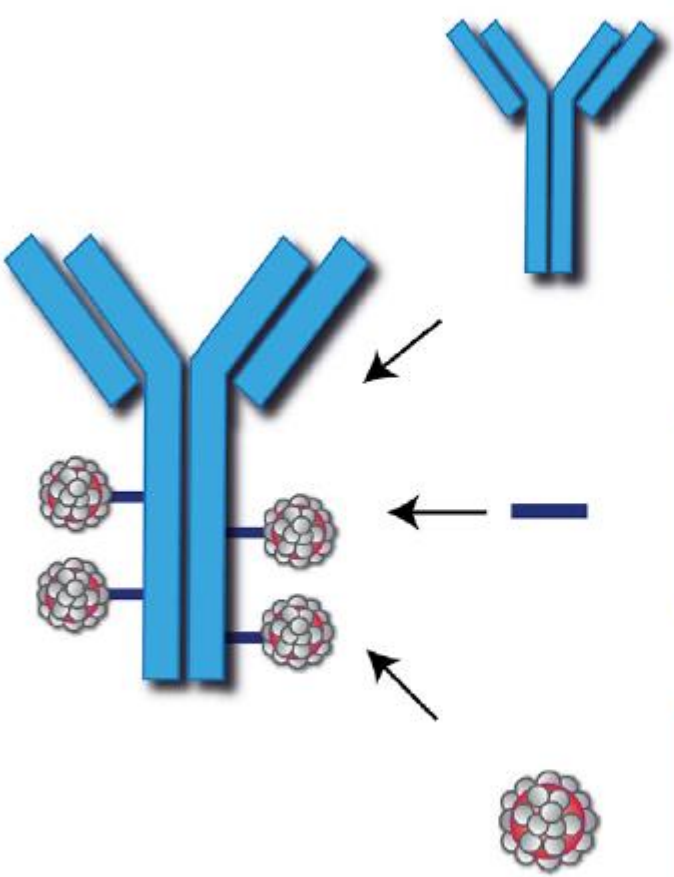
Onsum MD et al. Am J Path 2013

CLEOPATRA: final OS analysis



Swain SM, *et al*. ESMO 2014 (Abstract 350O) and NEJM 2015.

Modular components of an Antibody-Drug Conjugate (ADC)



The monoclonal antibodies, depending on its subtype backbone (IgG1, IgG2, IgG3, IgG4), present intrinsic properties that include serum half-life, Fcγ avidity and C1q binding. They target the ADC on the antigen.

The linkers are divided into cleavable (hydrazone, disulfide, dipeptide) and non-cleavable) and are needed to bound the payload to the mAb backbone.

The payloads consist in small molecules endow with pharmaco-logical effect. Upon their release, they either target DNA structure or tubulin polymerization to induce cell death by apoptosis

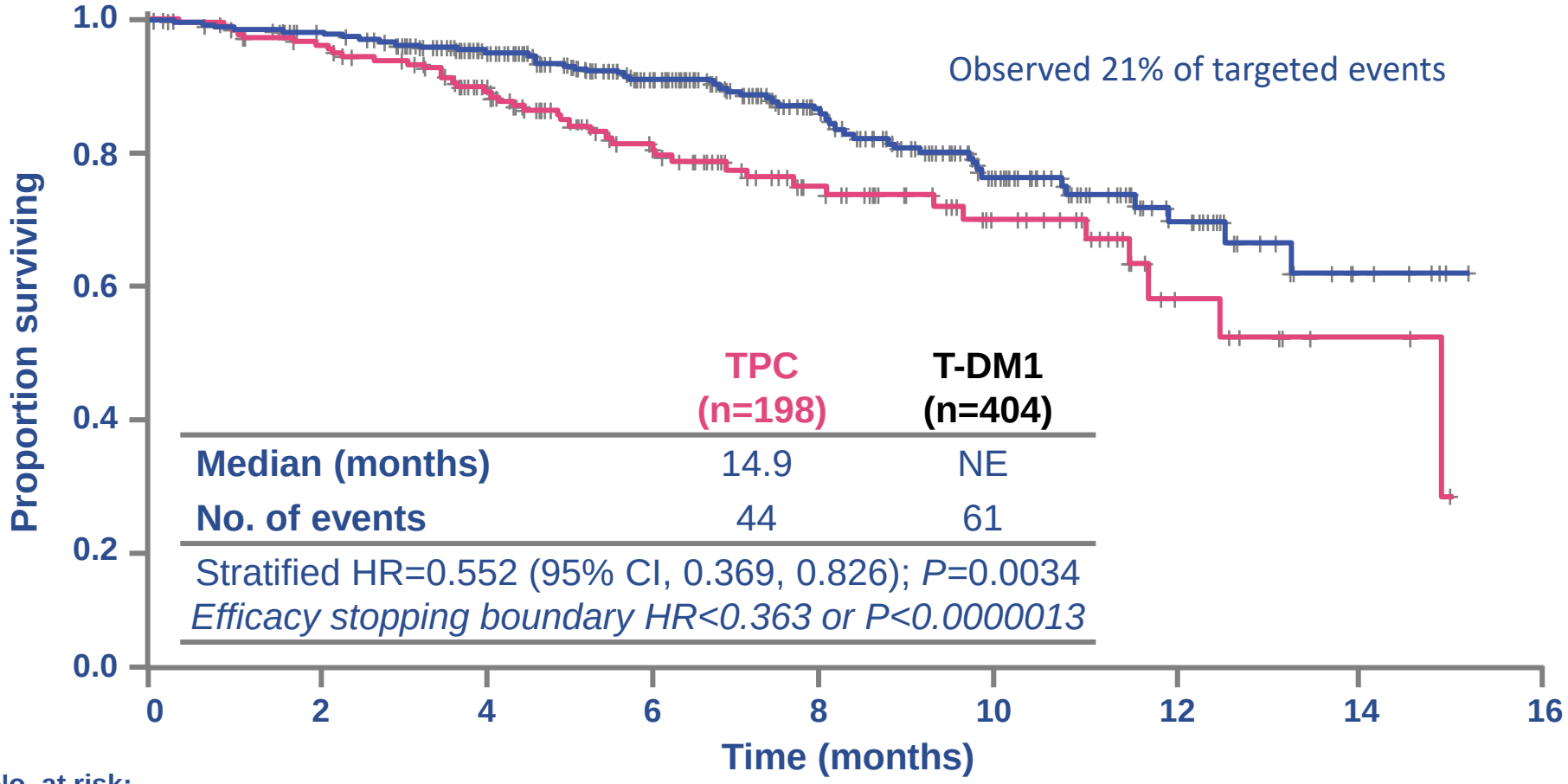
Riccardi F et al Frontiers in Pharmacology 2023

FDA/EMA approved ADCs in Clinical Oncology

ADC	Manufacturer	Trade name®	Target	FDA/EMA approval	Cancer
Gemtuzumab ozogamicin	Pfizer	Mylotarg	CD33	2000(2017)/2018	AML
Brentuximab vedotin	Seagen, Takeda Pharma	Adcetris	CD30	2011/2012	HL; sALCL
Inotuzumab ozogamicin	Pfizer	Besponsa	CD22	2017	B-cell prec. ALL
Polatuzumab vedotin	Genentech	Polivy	CD79b	2019/2020	DLBCL
Belantamab mafodotin	GlaxoSmithKline	Blenrep	BCMA	2020*	MM
Loncastuximab tesirine	ADC Therapeutics	Zynlonta	CD19	2021/2022	large B-cell prec. L
Moxetumomab pasudotox	AstraZeneca	Lumoxiti	PE38	2018	HCL
Ado-Trastuzumab Emtansine	Genentech	Kadcyla	HER2	2013	HER2+ e/m BC
Enfortumab vedotin	Astellas Pharma US, Seagen	Padcev	NECTIN4	2019/2022	mUC
Fam-trastuzumab Deruxtecan	Daichii Sankyo	Enhertu	HER2	2019/2021	HER2+ BC; NSCLC; GC/GOJ
Sacituzumab govitecan	Gilead Sciences	Trodelvy	TROP2	2020/2021	TNBC; mUC
Tisotumab vedotin-tftv	Seagen	Tivdak	TF	2021 (only FDA)	CC
Mirvetuximab Soravtansine	ImmunoGen	ELAHERE	FRα	2022 (only FDA)	OC
Disitamab Vedotin	Remegen	Aidixi**	HER2	—	UC; GC
Cetuximab Sarotalocan	Rakuten Medical	Akalux**	EGFR	—	HNSCC

Riccardi F et al Frontiers in Pharmacology 2023

TH3RESA
First Interim OS Analysis



	TPC (n=198)	T-DM1 (n=404)
Median (months)	14.9	NE
No. of events	44	61

Stratified HR=0.552 (95% CI, 0.369, 0.826); *P*=0.0034

Efficacy stopping boundary HR<0.363 or P<0.0000013

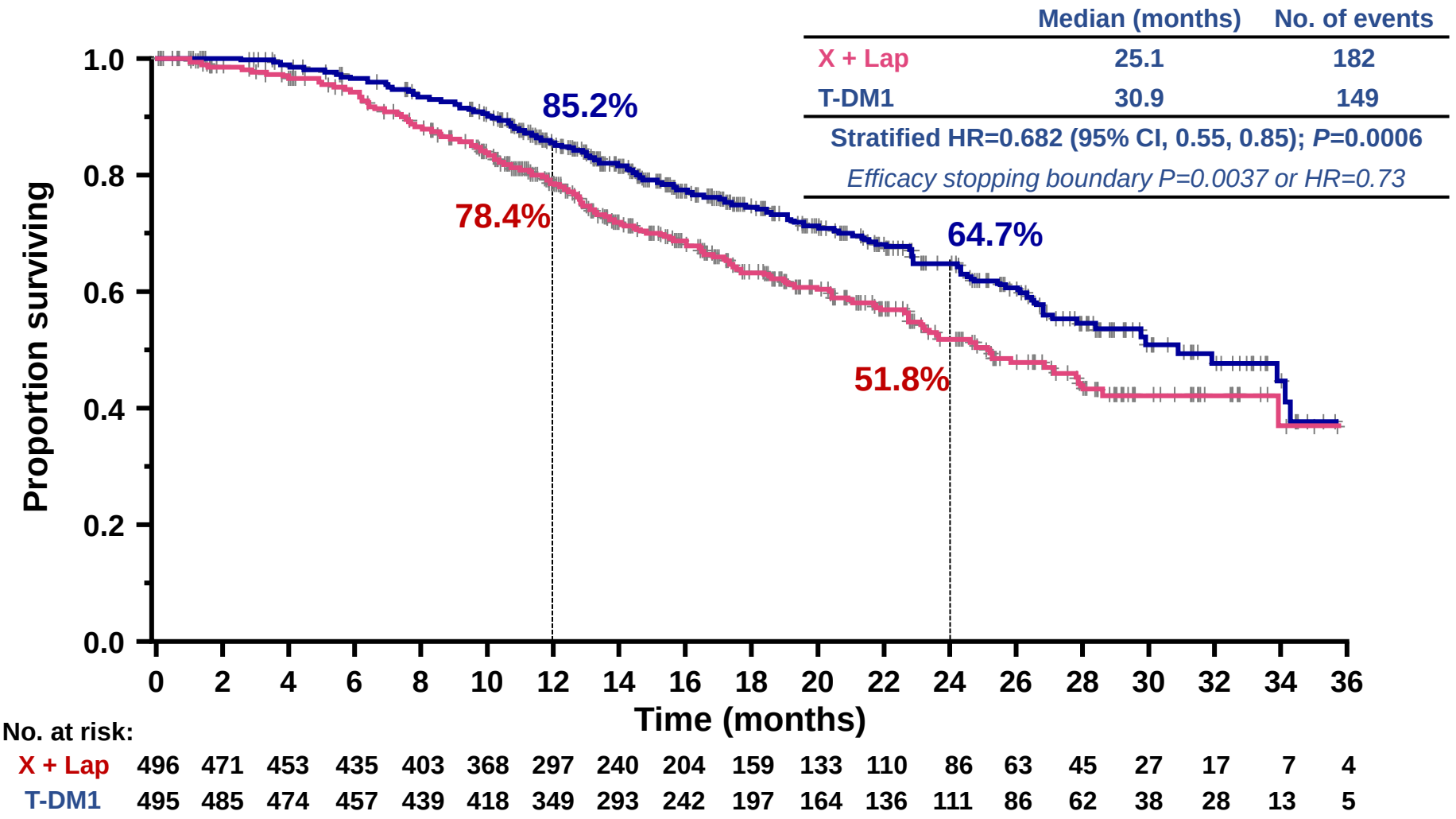
No. at risk:

TPC	198	169	125	80	51	30	9	3	0
T-DM1	404	381	316	207	127	65	30	7	0

44 patients in the TPC arm received crossover T-DM1 treatment after documented progression.

Krop I et al. Lancet 2014

EMILIA
Overall Survival: Confirmatory Analysis



Verma *et al*, NEJM, 1 October 2012

Trastuzumab emtansine: antibody drug conjugate

Antibody

Target expression: HER2

Humanised mAb
Trastuzumab

Drug

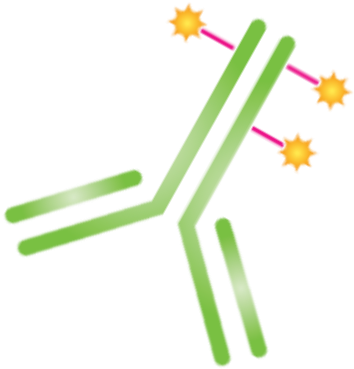
Cytotoxic drug: DM1*

Highly potent cytotoxic agent (tubulin destabiliser)

Conjugate

Nonreducible thioether linker: SMCC

Systemically stable



Trastuzumab emtansine

*derivative of mytansine

Maytansine causes apoptosis through inhibition of microtubule assembly

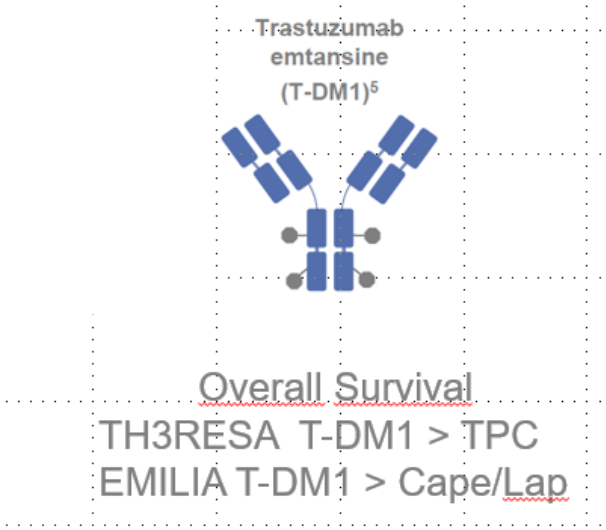
Burris HA. Expert Opin Biol Ther 2011; 11(6): 807-819.

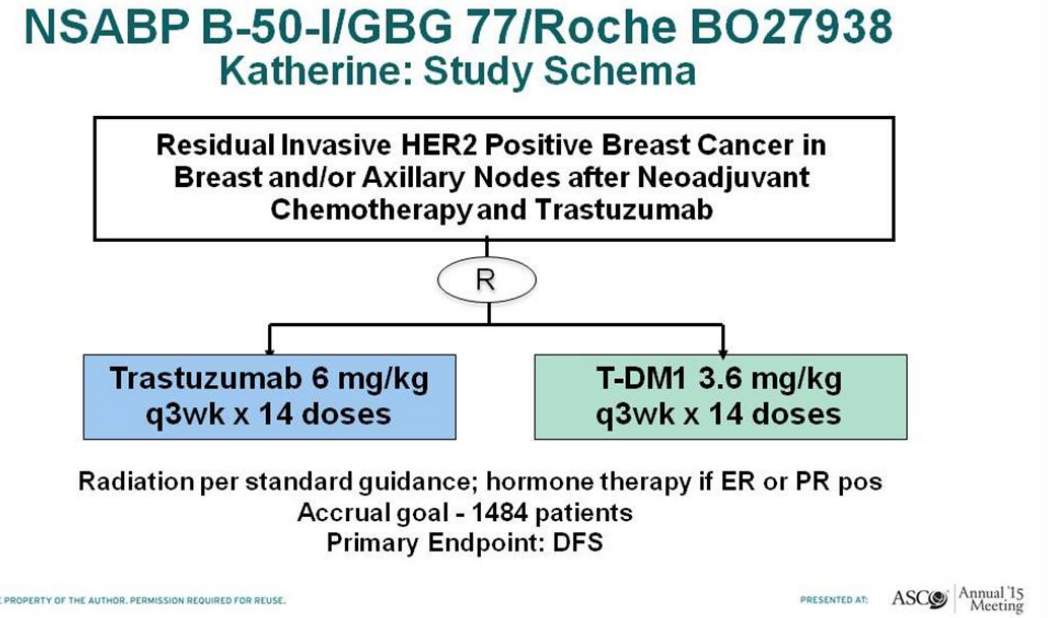
Tappe fondamentali della terapia anti HER-2

1998 l'inizio

2005 la rivoluzione

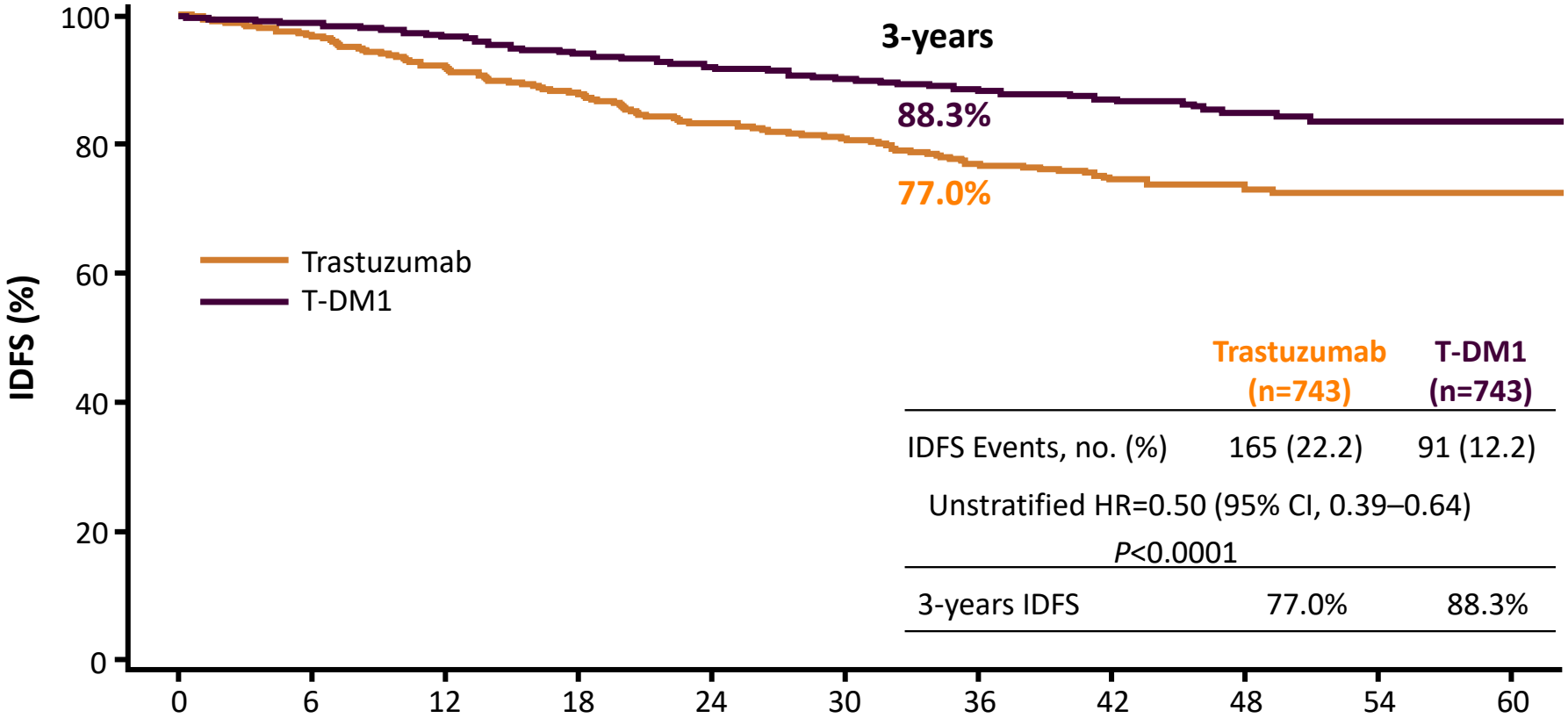
2019 il nuovo paradigma





von Minckwitz G et al ASCO 2015
von Minckwitz G et al NEJM 2019

KATHERINE: Kaplan-Meier Plot of IDFS (ITT)



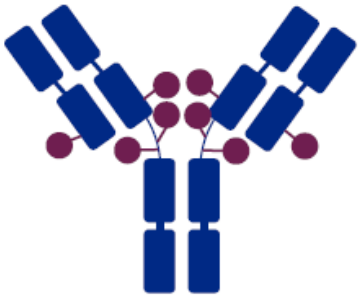
	Trastuzumab (n=743)	T-DM1 (n=743)
IDFS Events, no. (%)	165 (22.2)	91 (12.2)
Unstratified HR=0.50 (95% CI, 0.39–0.64) *P*<0.0001		
3-years IDFS	77.0%	88.3%

Trastuzumab	743	676	635	594	555	501	342	220	119	38	4
TDM-1	743	707	681	658	633	561	409	255	142	44	4

Geyer CE et al SABCS 2018,
von Minckwitz G et al NEJM 2019

ADC Characteristic

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes
Topoisomerase I inhibitor	**Payload MoA**
~8:1	**Drug-to-antibody ratio**
Yes	**Tumor-selective cleavable linker?**
Yes	**Evidence of bystander anti-tumor effect?**

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

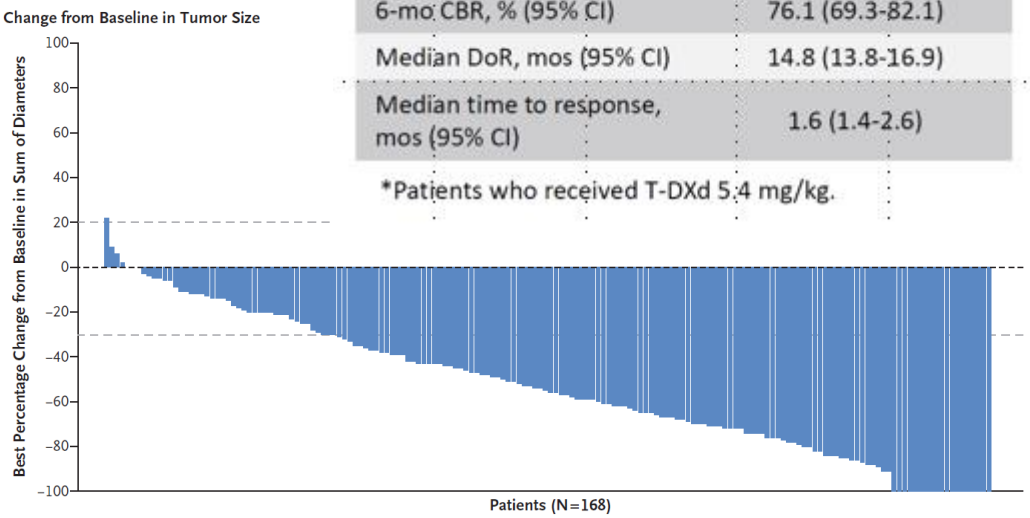
S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

Median no. of previous cancer regimens (range)	6 (2–27)
Previous systemic cancer therapy — no. (%)	
Trastuzumab	184 (100)
Trastuzumab emtansine¶	184 (100)
Pertuzumab	121 (65.8)
Other anti-HER2 therapy	100 (54.3)
Hormone therapy	90 (48.9)
Other systemic therapy	183 (99.5)

Response (ITT)	T-DXd 5.4 mg/kg (N = 184)
ORR* (by ICR; n = 112), % (95% CI)	60.9 (53.4-68.0)
▪ CR (n = 11)	6.0
▪ PR (n = 101)	54.9
▪ SD (n = 67)	36.4
▪ PD (n = 3)	1.6
▪ Not evaluable (n = 2)	1.1
DCR, % (95% CI)	97.3 (93.8-99.1)
6-mo CBR, % (95% CI)	76.1 (69.3-82.1)
Median DoR, mos (95% CI)	14.8 (13.8-16.9)
Median time to response, mos (95% CI)	1.6 (1.4-2.6)

*Patients who received T-DXd 5.4 mg/kg.

Median DOR 14.8 mo.s
Median PFS 16.4 mo.s
12-mo.s OS 86.2% (median not reached)



N Engl J Med 2020;382:610-21.

DESTINY-Breast02

Randomized phase 3, open-label, multicenter study (NCT03523585)

Key eligibility criteria[a]
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
or
- Lapatinib / Capecitabine

Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

At data cutoff (June 30, 2022), the median duration of follow-up[d] was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

Protocol-prespecified statistical analysis plan
- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

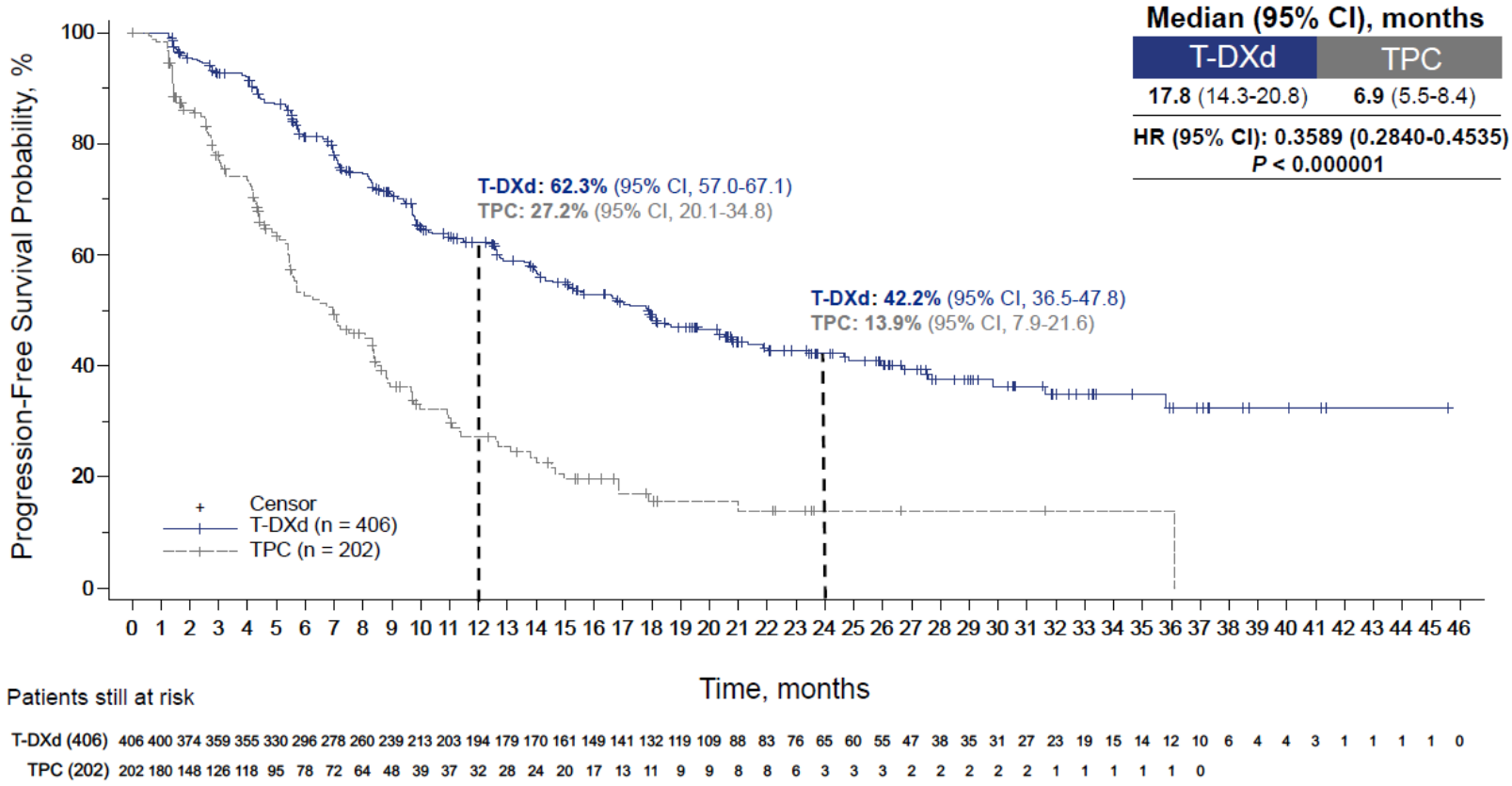
BICR, blinded independent central review; CBR, clinical benefit rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mRECIST, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2; progression-free survival on the next line of therapy; Q3W, every 3 weeks; R, randomization, T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]BICR assessed per mRECIST 1.1. [c]PFS2 was defined as the time from date of randomization to the first documented progression on the next line of therapy or death due to any cause, whichever came first. [d]Duration of follow up is defined as study duration = the date last known alive minus date of randomization plus 1.

Prior Therapies

Prior Treatment	T-DXd n = 406	TPC n = 202
Prior treatment for BC, n (%)	406 (100)	202 (100)
Prior lines of therapy in the metastatic setting,[a] n (%)		
0	2 (0.5)	0
1	18 (4.4)	12 (5.9)
2	192 (47.3)	92 (45.5)
3	123 (30.3)	63 (31.2)
4	42 (10.3)	13 (6.4)
≥5	29 (7.1)	22 (10.9)
Median number of prior lines of systemic therapy in the metastatic setting,[a] (range)	2 (0-10)	2 (1-8)
Prior systemic cancer therapy, n (%)		
Trastuzumab	404 (99.5)	202 (100)
T-DM1	404 (99.5)	202 (100)
Taxane	386 (95.1)	197 (97.5)
Pertuzumab	318 (78.3)	156 (77.2)
Other systemic therapy	289 (71.2)	157 (77.7)
Hormone therapy	164 (40.4)	87 (43.1)
Anti-HER2 TKI	26 (6.4)	17 (8.4)
Other anti-HER2 therapy (except HER2 TKI)	11 (2.7)	6 (3.0)

BC, breast cancer; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; TPC, treatment of physician's choice.
[a]Includes regimens indicated for advanced/metastatic disease or rapid progression within 6 months of (neo)adjuvant (12 months for pertuzumab) therapy. Line of therapy does not include hormone therapy.

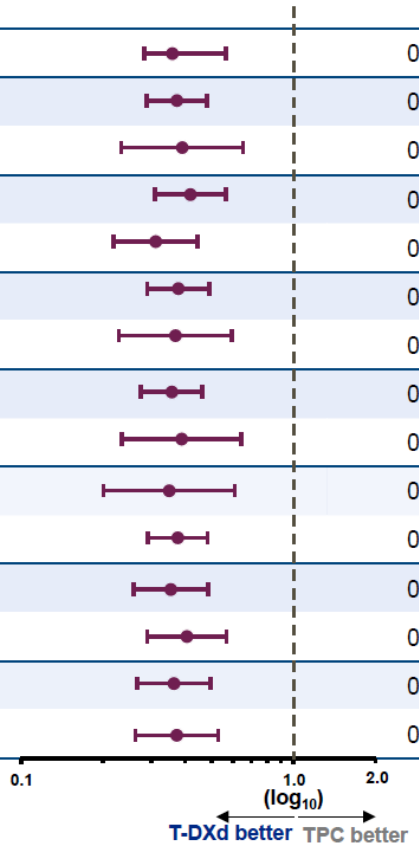
Primary Endpoint: PFS by BICR



BICR, blinded independent central review; HR, hazard ratio; mo, month; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS in Key Subgroups

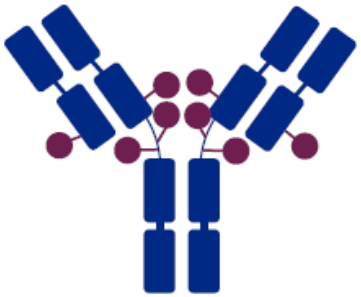
		Number of Events		Median PFS, mo (95% CI)		HR (95% CI)
		T-DXd	TPC	T-DXd	TPC	
All patients		200/406	125/202	17.8 (14.3-20.8)	6.9 (5.5-8.4)	0.36 (0.28-0.45)
Age	<65	160/321	101/164	17.9 (14.1-20.8)	7.1 (5.5-8.6)	0.37 (0.29-0.48)
	≥65	40/85	24/38	16.8 (12.7-NE)	6.7 (4.3-8.4)	0.39 (0.23-0.65)
Hormone receptor status	Positive	115/238	71/118	18.0 (15.1-21.3)	8.5 (6.5-10.0)	0.42 (0.31-0.57)
	Negative	84/165	53/83	17.0 (12.3-24.6)	5.3 (4.3-6.7)	0.31 (0.22-0.45)
Prior pertuzumab treatment[a]	Yes	155/318	95/156	17.8 (14.0-20.8)	6.2 (5.0-8.4)	0.38 (0.29-0.49)
	No	45/88	30/46	18.0 (13.9-26.7)	8.3 (5.5-12.6)	0.37 (0.23-0.60)
Visceral disease[a]	Yes	164/316	98/160	15.6 (12.8-20.3)	5.7 (5.3-7.2)	0.36 (0.28-0.46)
	No	36/90	27/42	29.8 (16.8-NE)	9.8 (6.2-12.6)	0.39 (0.23-0.64)
Baseline brain metastases	Yes	44/74	20/36	13.9 (11.1-18.0)	5.6 (3.3-8.1)	0.35 (0.20-0.61)
	No	156/332	105/166	18.7 (15.1-24.8)	7.1 (5.5-8.6)	0.38 (0.29-0.48)
Prior lines of therapy[b]	<3	105/212	66/104	16.6 (13.8-24.6)	7.0 (4.6-8.6)	0.35 (0.26-0.49)
	≥3	95/194	59/98	18.2 (14.3-22.0)	6.9 (5.5-8.8)	0.41 (0.29-0.57)
ECOG PS	0	101/228	75/121	24.6 (15.3-31.6)	8.1 (5.7-9.7)	0.36 (0.27-0.50)
	1	98/177	50/81	15.1 (11.5-18.0)	5.4 (4.3-7.5)	0.37 (0.26-0.53)



ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mo, months; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Subgroup values are derived from baseline. [b]Lines of prior systemic therapy not including hormone therapy.

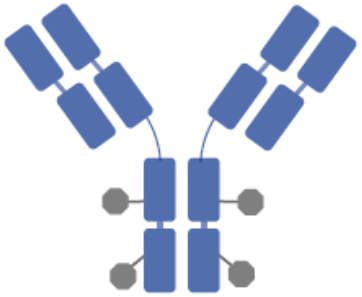
ADC Characteristic Differences Between T-DXd and T-DM1

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]



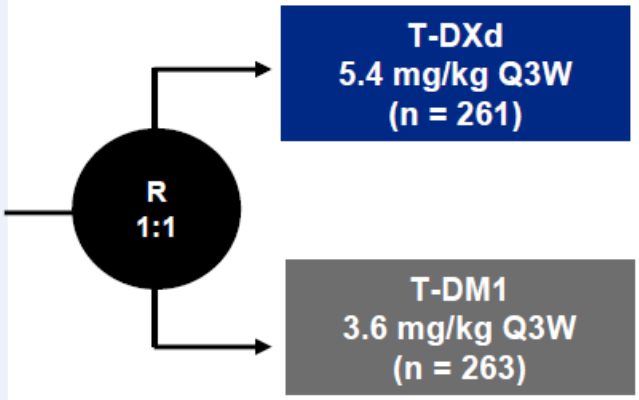
Overall Survival
TH3RESA T-DM1 > TPC
EMILIA T-DM1 > Cape/Lap

DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

An open-label, multicenter study (NCT03529110)

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

Cortès J et al ESMO 2021

Prior Therapies

	T-DXd (n = 261)	T-DM1 (n = 263)
Prior Treatment for mBC, n (%)		
No	21 (8.0)	29 (11.0)
Yes	240 (92.0)	234 (89.0)
Prior lines of therapy in the metastatic setting (includes rapid progressors as one line of treatment)[a], n (%)		
0	2 (0.8)	3 (1.1)
1	130 (49.8)	123 (46.8)
2	56 (21.5)	65 (24.7)
3	35 (13.4)	35 (13.3)
4	15 (5.7)	19 (7.2)
≥5	23 (8.8)	18 (6.8)
Prior cancer therapy[b], %		
Trastuzumab	99.6	99.6
Pertuzumab	62.1	60.1
Other anti-HER2		
Anti-HER2 TKI	16.1	13.7
Other anti-HER2 antibody or ADC	0.8	1.1

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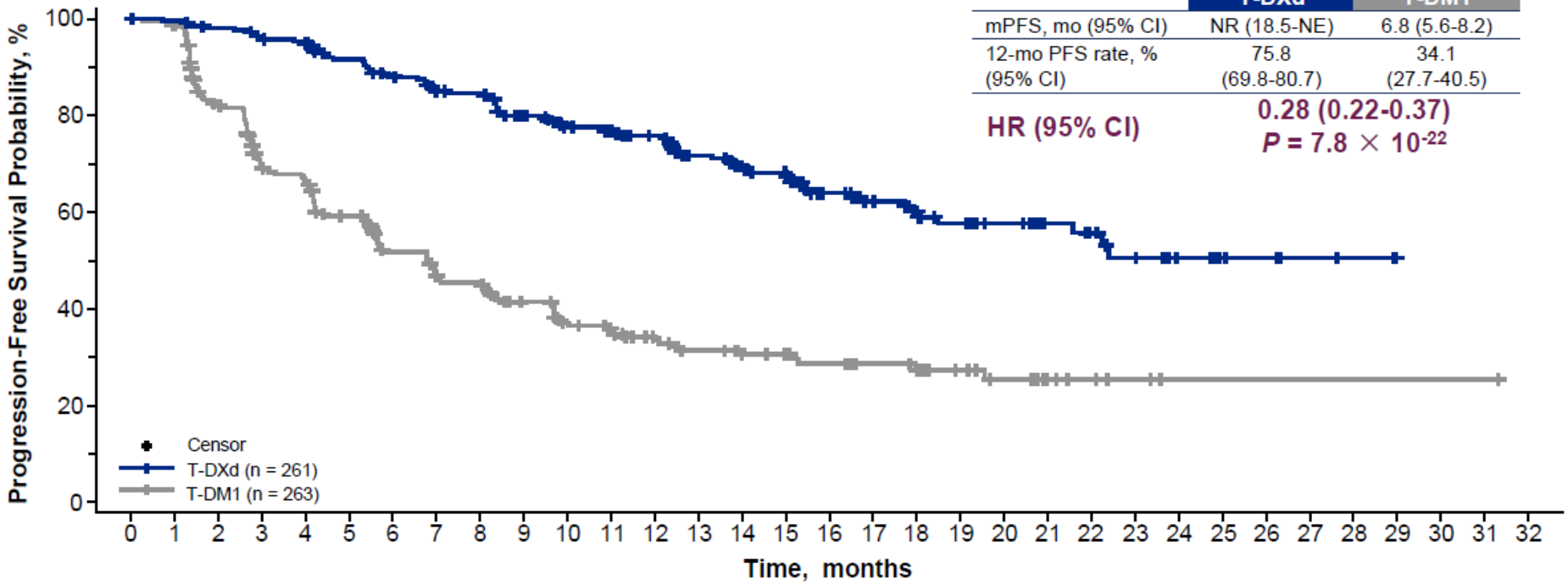
Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0	
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

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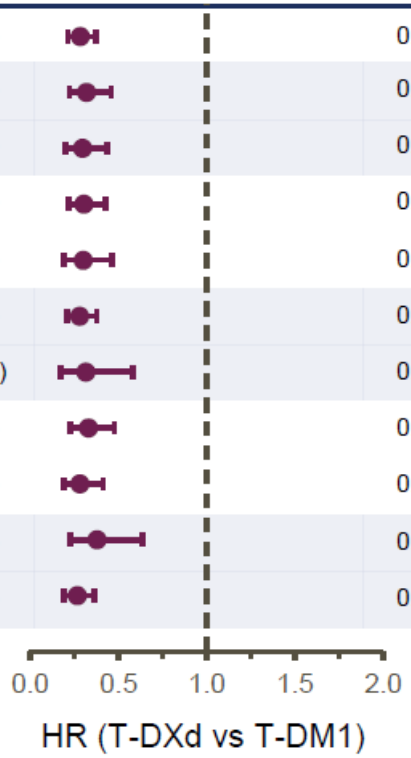
PFS in Key Subgroups

		Number of Events		Median PFS (mo, 95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone Receptor Status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior Pertuzumab Treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral Disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior Lines of Therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
Brain Metastases	Yes (n = 114)	31/62	31/52	15.0 (12.6-22.2)	5.7 (2.9-7.1)	0.3796 (0.2267-0.6357)
	No (n = 410)	56/199	127/211	NE (22.4-NE)	7.0 (5.5-9.7)	0.2665 (0.1939-0.3665)



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[a]Rapid progressors on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.

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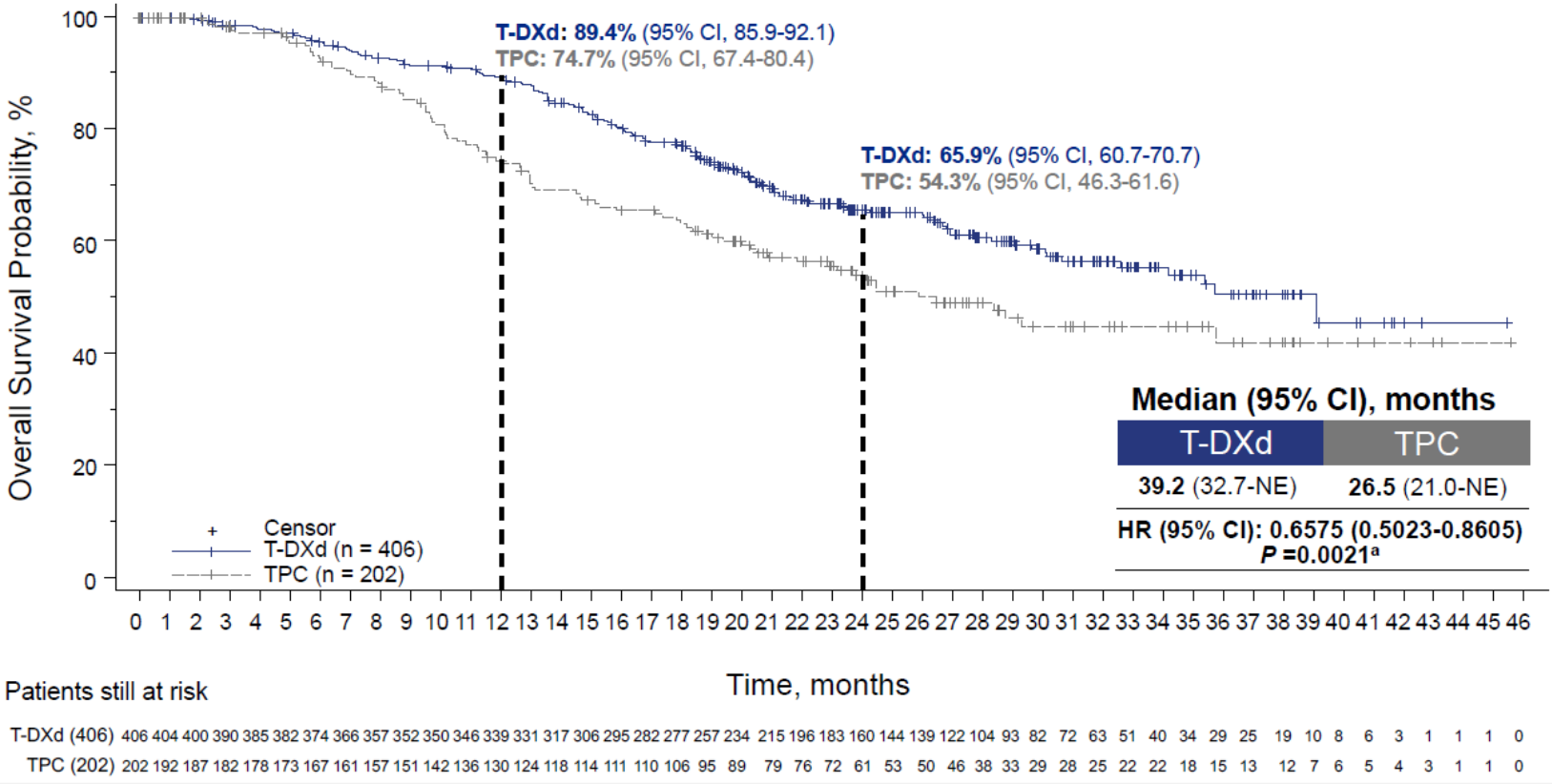
Key Secondary Endpoint: OS



In the TPC arm

- **69.3% (140/202) of patients received a new systemic anticancer treatment**
- **25.7% (52/202) of patients received T-DXd in the post-trial setting**

[a]The boundary for statistical significance is 0.0040. HR, hazard ratio; mo, month; NE, not estimable; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Drug-Related TEAEs in ≥20% of Patients

System Organ Class Preferred term, n (%)	T-DXd (n = 257) Any Grade	T-DXd (n = 257) Grade ≥3	T-DM1 (n = 261) Any Grade	T-DM1 (n = 261) Grade ≥3
Blood and lymphatic system disorders				
Neutropenia[a]	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia[b]	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia[c]	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia[d]	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue[e]	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
ALT increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia[f]	93 (36.2)	1 (0.4)	6 (2.3)	0

Most drug-related TEAEs were gastrointestinal or hematological in nature

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF decrease, n (%)						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

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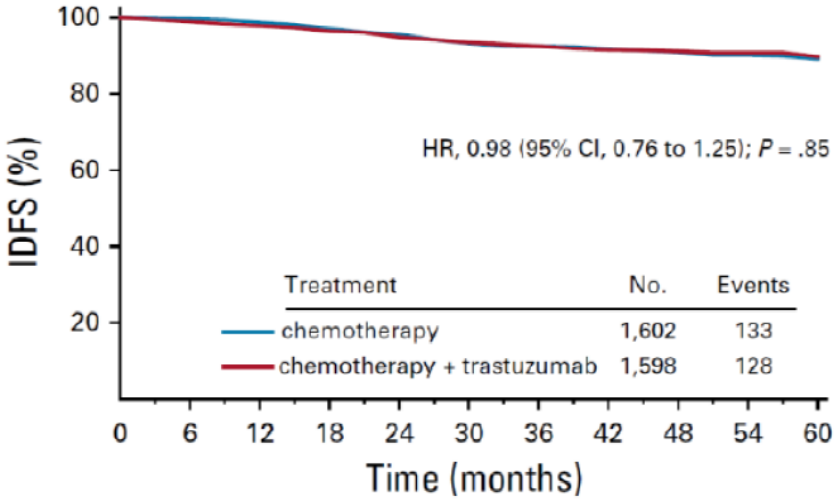
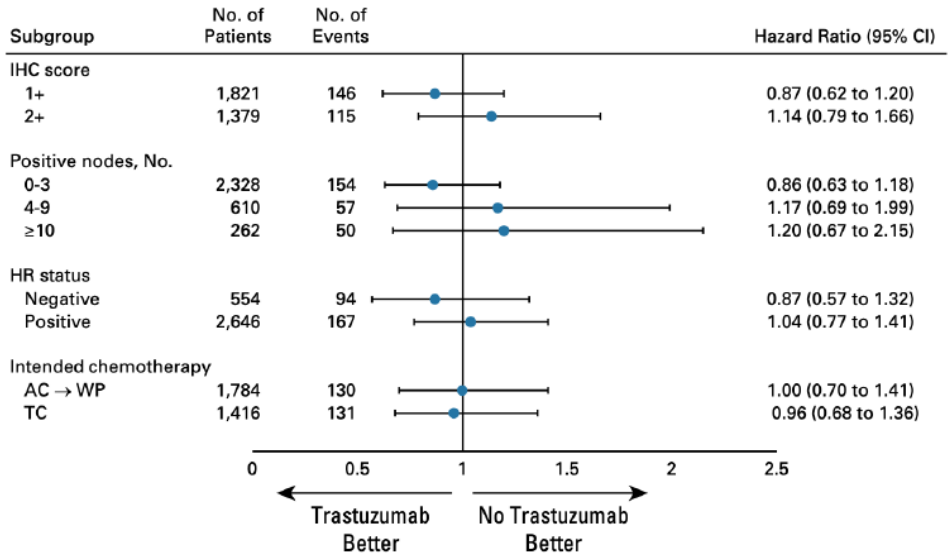
Trastuzumab is NOT effective in HER2-low eBC

NSABP B-47 iDFS

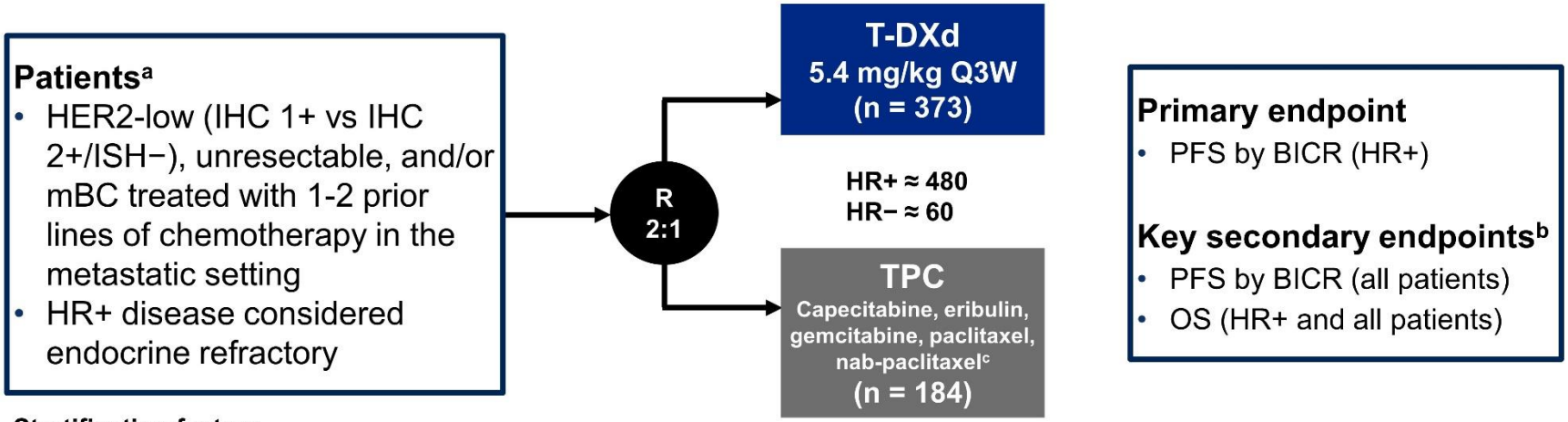




Fehrenbacher L et al J Clin Oncol 2020

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

An open-label, multicenter study (NCT03734029)



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−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

Baseline Characteristics

	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)

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Hormone receptor status is based on data collected using the interactive web/voice response system at the time of randomization, which includes misstratified patients.

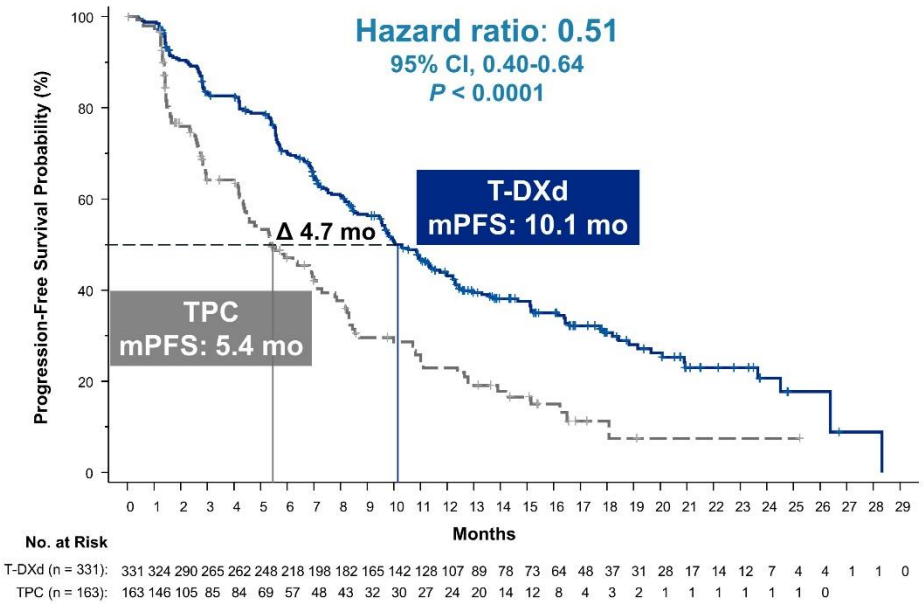
Prior Therapies

	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)

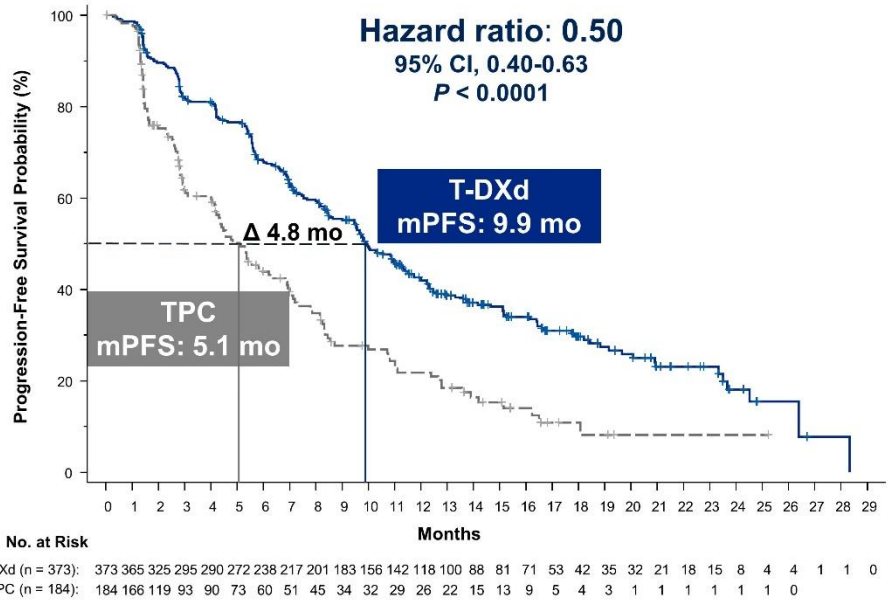
Based on derived data, which includes protocol deviations. CDK, cyclin-dependent kinase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS in HR+ and All Patients

Hormone receptor–positive



All patients

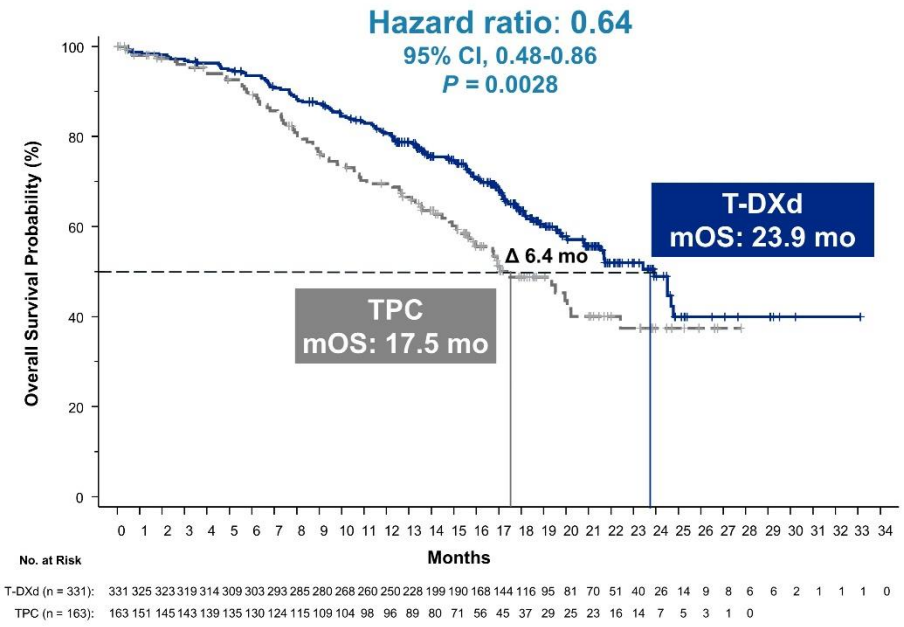


PFS by blinded independent central review.

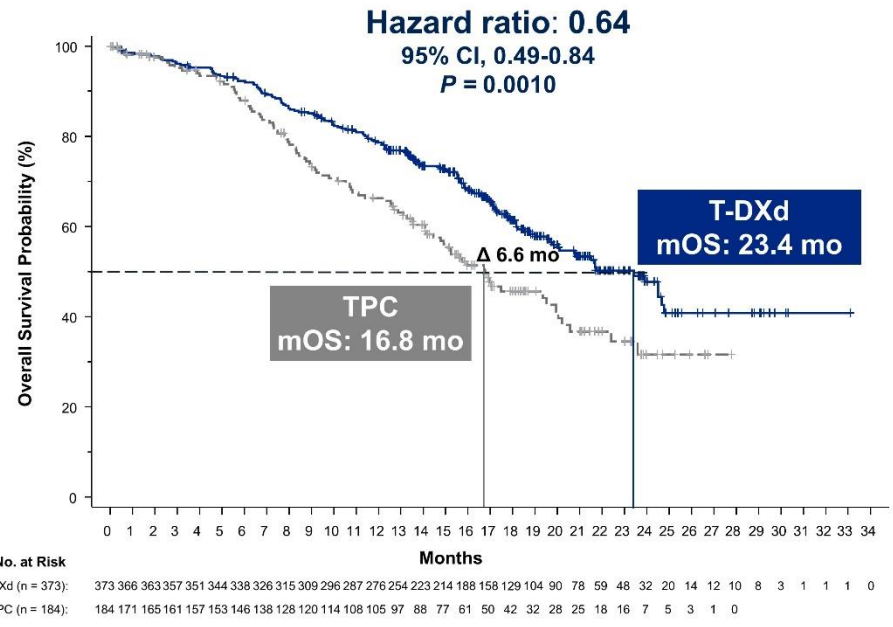
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

Hormone receptor–positive



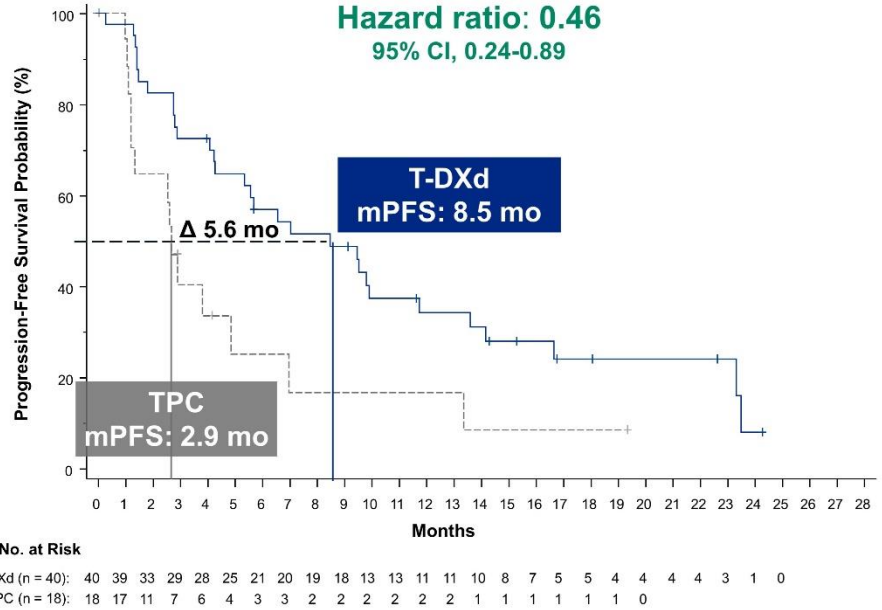
All patients



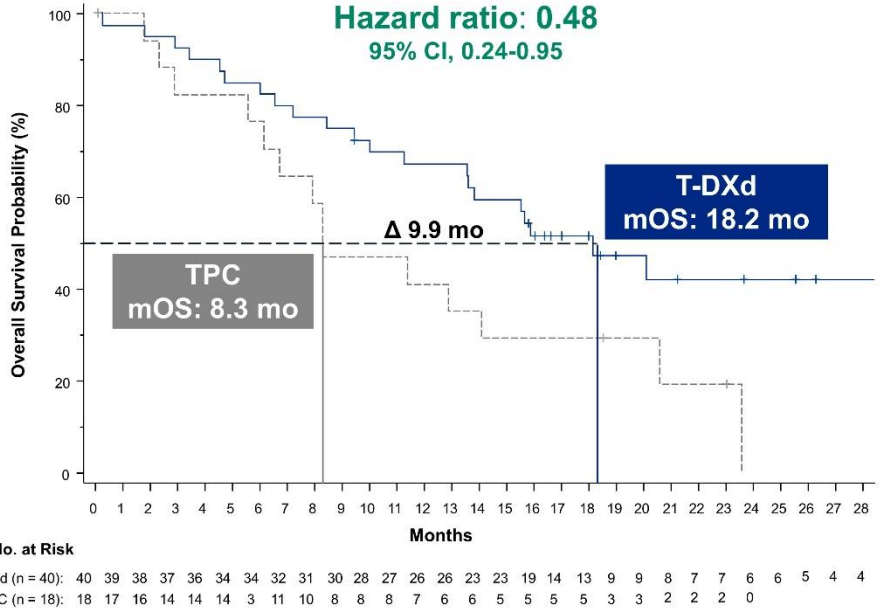
HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS and OS in HR− (Exploratory Endpoints)

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.

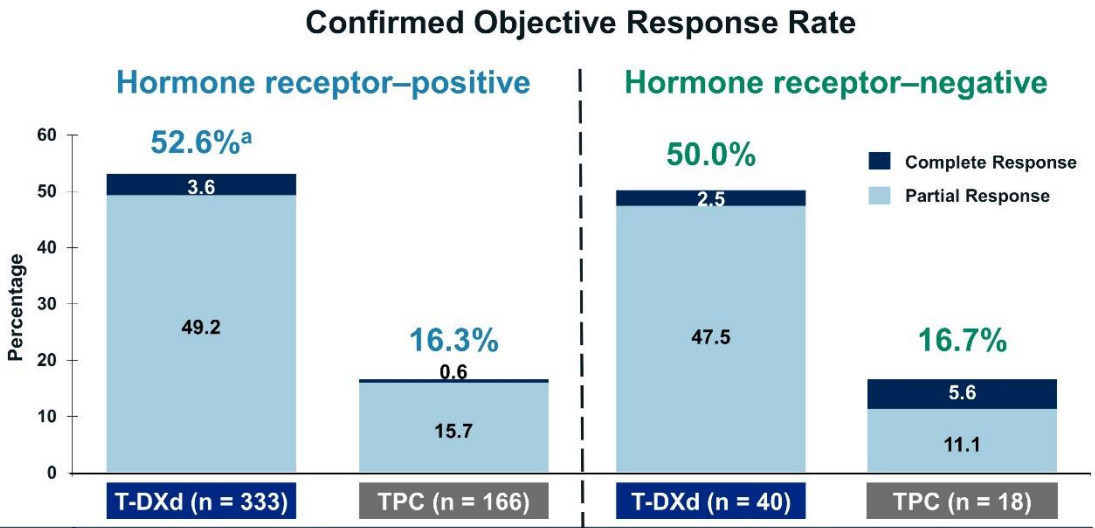
Subgroup Analysis: PFS in HR+

	No. of Events/No. of Patients T-DXd	TPC	PFS, median (95% CI), mo T-DXd	TPC	Hazard Ratio for Disease Progression or Death (95% CI)
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.

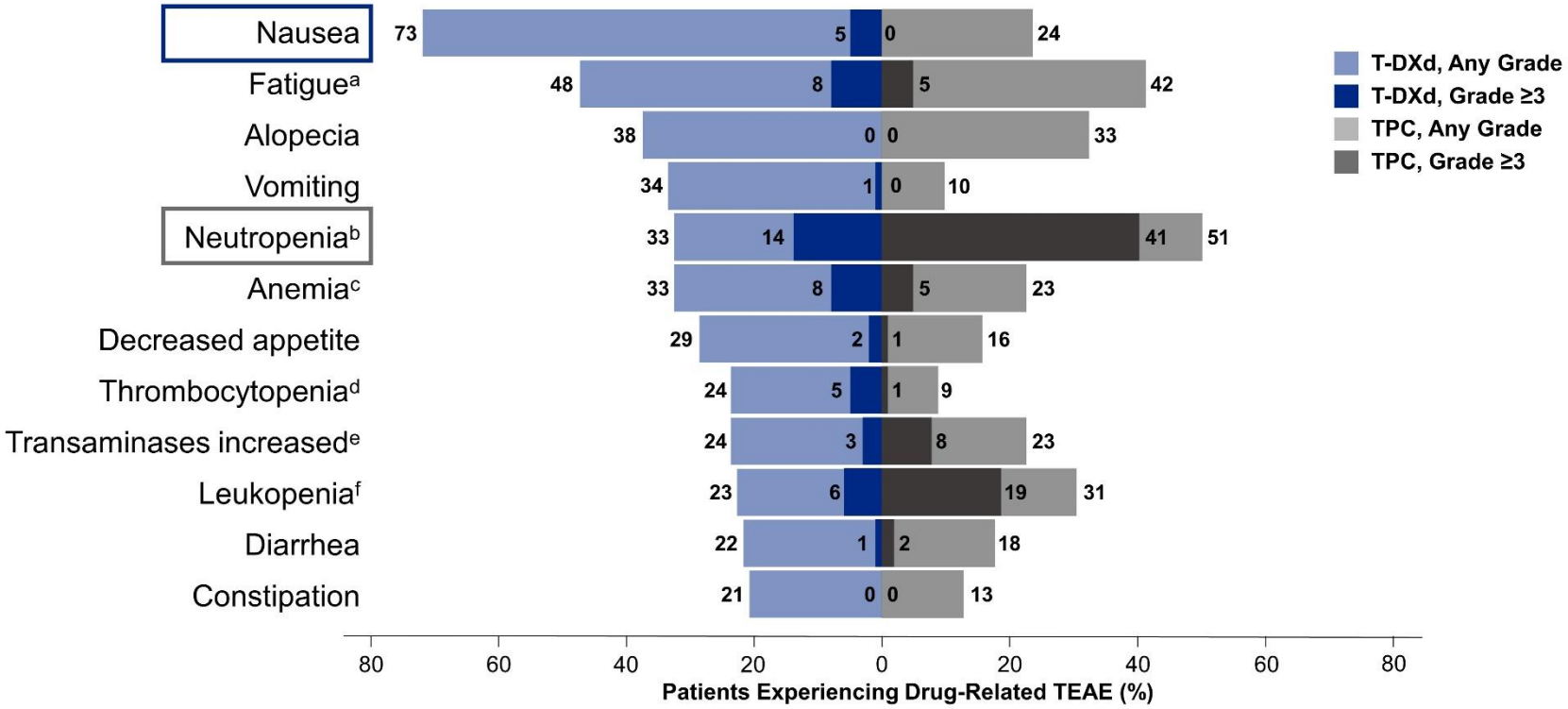
Confirmed ORR



	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.

Drug-Related TEAEs in ≥20% of Patients



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

Adverse Events of Special Interest

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)

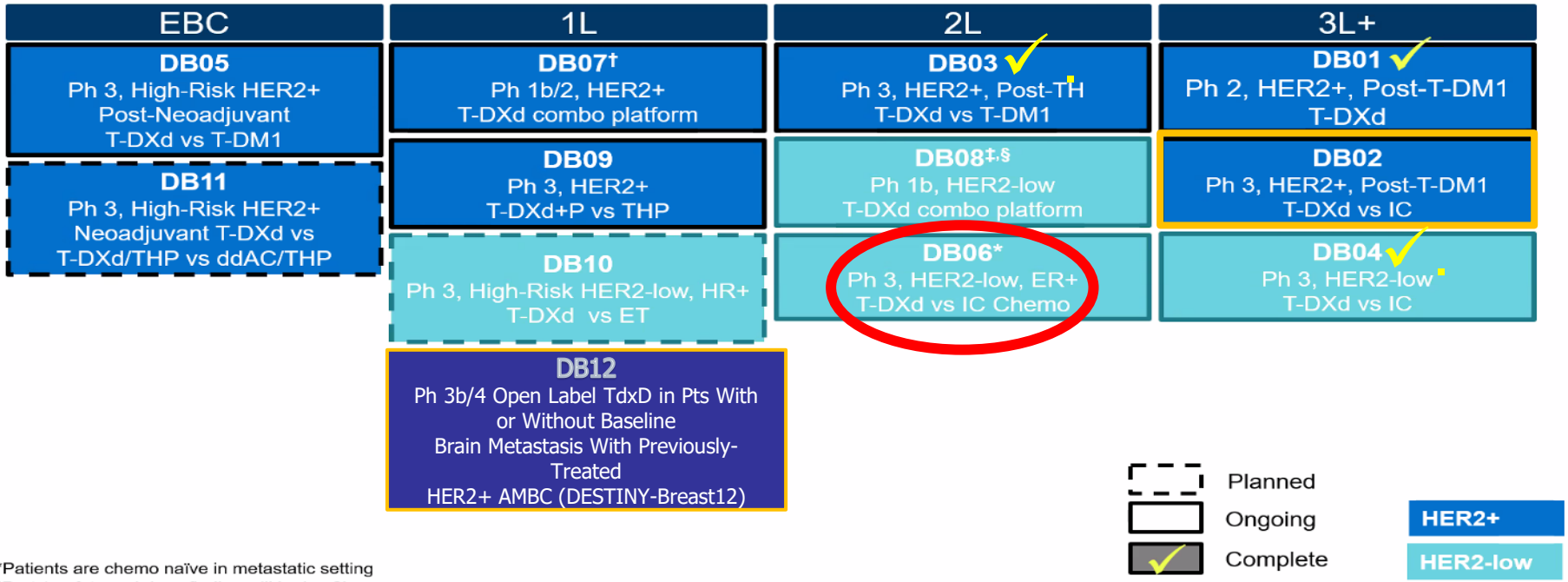
Left ventricular dysfunction[b]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Ejection fraction decreased						
T-DXd (n = 371)	1 (0.3)	14 (3.8)	1 (0.3)	0	0	16 (4.3)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure[c]						
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

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in the T-DXd arm. One patient initially experienced ejection fraction decrease, then later developed cardiac failure. [c]Both patients with cardiac failure were reported to have recovered.

Programma Breast T-Dxd

DESTINY-Breast Program Overview



*Patients are chemo naïve in metastatic setting
†Part 1 safety and dose finding will be in ≥2L

ADCs to target MBC: Multiple Agents in Development

Antibody Drug Conjugate	Target	Payload
Trastuzumab deruxtecan (DS-8201a)	HER2	Topo-1 inhibitor
Sacituzumab govitecan (IMMU-132)	Trop-2	Topo-1 inhibitor
Datopotamab deruxtecan (DS-1062)	Trop-2	Topo-1 inhibitor
Ladiratuzumab vedotin (SGN-LIV1a)	LIV-1	Microtubule inhibitor
Patritumab deruxtecan (U3-1402)	HER3	Topo-1 inhibitor
Trastuzumab duocarmazime	HER2	Alkylating agent
Disitimab vedotin	HER2	Microtubule inhibitor

Both target and payload important considerations for efficacy/toxicity profile and ADC sequencing

Bardia A, EBCC 2022