Optimizing Treatment of Metastatic HER2 Positive Breast Cancer

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Disclosures

- No current relevant COI
- Was a Consultant for Puma in 2020.
- Was on the Speakers Bureau for Puma in 2020 and SeaGen in 2021.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their products and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

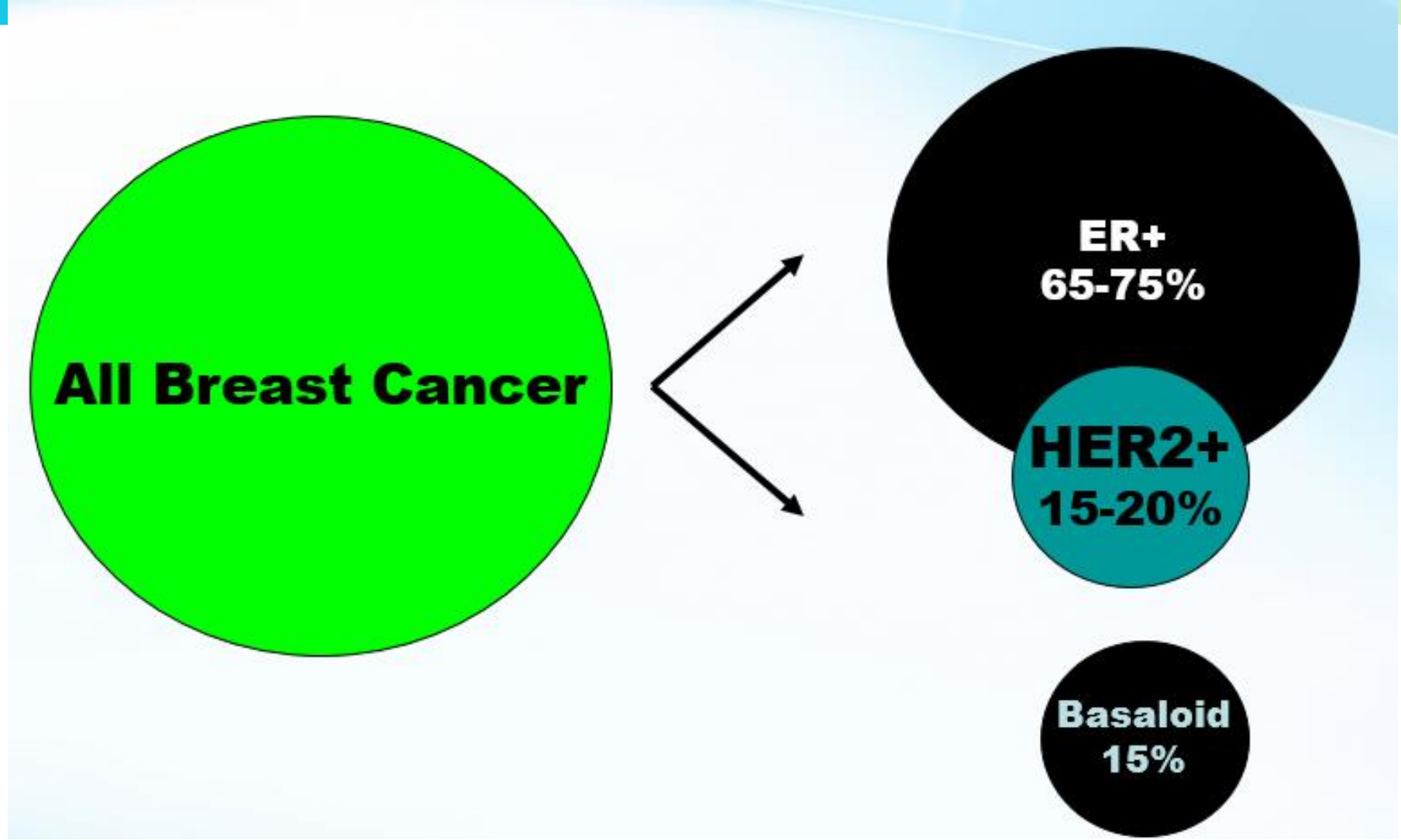
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- Access to the clinical trials in HER2 positive disease in minority groups.
- Racial disparities in receiving treatment and the outcomes of metastatic HER2 positive breast cancer.

OUTLINE

- Incidence and prognosis of metastatic HER2 positive breast cancer
- New treatment options for metastatic HER2 positive breast cancer
- Ongoing studies in HER2 positive MBC
- Future directions



20-30% of early-stage breast cancer patients develop metastasis

6-10% of patients have MBC at the time of diagnosis

MBC = metastatic breast cancer.
American Cancer Society (2016).

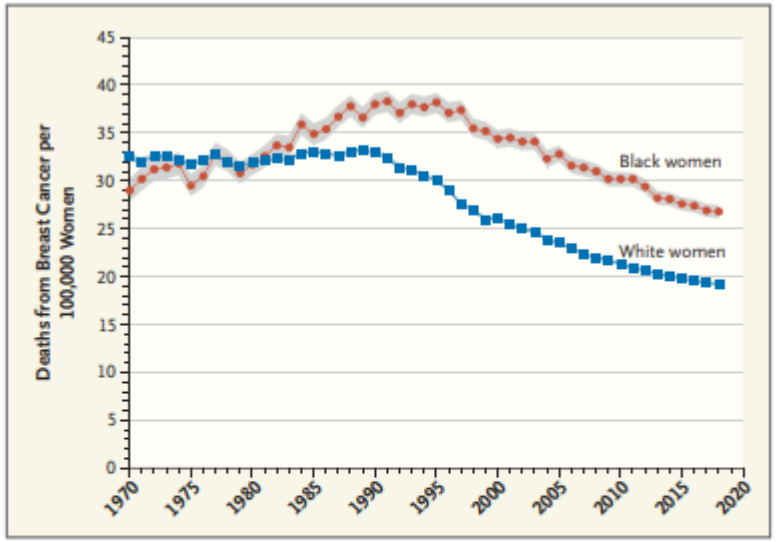
Racial Disparity in US Breast Cancer Mortality

- Breast cancer mortality was slightly lower among black women before 1980
- The death rates diverged sharply after 1980 (HR+, 19% higher in AA and triple negative more than twice higher)
- Multifactorial including limited access of black women to screening mammography and lack of access to new medical interventions
- 81% higher rate of triple negative BC in black women compared to non-Hispanic whites (21.9 vs. 12.1 cases per 100,000)

Incidence of Breast Cancer and Breast-Cancer Mortality among Black Women and Non-Hispanic White Women in the United States According to HR Status, 2014 through 2018.*

Variable	Black Women		Non-Hispanic White Women		Difference	
	No. of Cases (%)	Cases per 100,000 Women (95% CI)	No. of Cases (%)	Cases per 100,000 Women (95% CI)	Cases per 100,000 Women (95% CI)	Incidence Rate Ratio (95% CI)
Incidence						
Any HR status	17,025 (100)	125.8 (123.9 to 127.8)	103,332 (100)	139.2 (138.3 to 140.1)	−13.38 (−15.51 to −11.25)	0.90 (0.89 to 0.92)
HR-positive status	12,458 (73)	92.1 (90.4 to 93.7)	87,865 (85)	118.0 (117.2 to 118.9)	−25.99 (−27.83 to −24.14)	0.78 (0.77 to 0.80)
HR-negative status	3,985 (23)	29.3 (28.4 to 30.2)	12,614 (12)	17.7 (17.4 to 18.1)	11.56 (10.57 to 12.54)	1.65 (1.59 to 1.71)
HR status borderline or unknown	582 (3)	4.5 (4.1 to 4.9)	2,853 (3)	3.4 (3.3 to 3.6)	1.05 (0.66 to 1.45)	1.31 (1.19 to 1.43)
	No. of Deaths (%)	Deaths per 100,000 Women (95% CI)	No. of Deaths (%)	Deaths per 100,000 Women (95% CI)	Deaths per 100,000 Women (95% CI)	Mortality Rate Ratio (95% CI)
Death certificate–based mortality	3,694 (100)	27.7 (26.8 to 28.6)	16,384 (100)	20.0 (19.7 to 20.4)	7.64 (6.67 to 8.60)	1.38 (1.33 to 1.43)
Incidence-based mortality						
Any HR status	3,575 (100)	26.6 (25.8 to 27.6)	15,274 (100)	18.8 (18.5 to 19.1)	7.83 (6.89 to 8.78)	1.42 (1.36 to 1.47)
HR-positive status	2,159 (60)	16.1 (15.4 to 16.8)	11,017 (72)	13.5 (13.3 to 13.8)	2.55 (1.81 to 3.30)	1.19 (1.13 to 1.25)
HR-negative status	1,077 (30)	8.0 (7.5 to 8.5)	2,743 (18)	3.6 (3.4 to 3.7)	4.39 (3.88 to 4.89)	2.23 (2.07 to 2.40)
HR status borderline or unknown	339 (9)	2.6 (2.3 to 2.9)	1,514 (10)	1.7 (1.6 to 1.8)	0.89 (0.59 to 1.19)	1.52 (1.35 to 1.71)

* Data are from the Surveillance, Epidemiology, and End Results (SEER) registries, which cover 13.4% of the U.S. population. Black women include Hispanic and non-Hispanic Black women. Differences in rates were calculated with the use of the National Cancer Institute's Health Disparities Calculator. Incidence-based mortality was estimated among breast cancers diagnosed from 1992 through 2018 and within 21 years before death in the SEER 13 registry database. Cases identified from only autopsy records or death certificates were excluded. Percentages may not total 100 because of rounding. CI denotes confidence interval and HR hormone receptor.



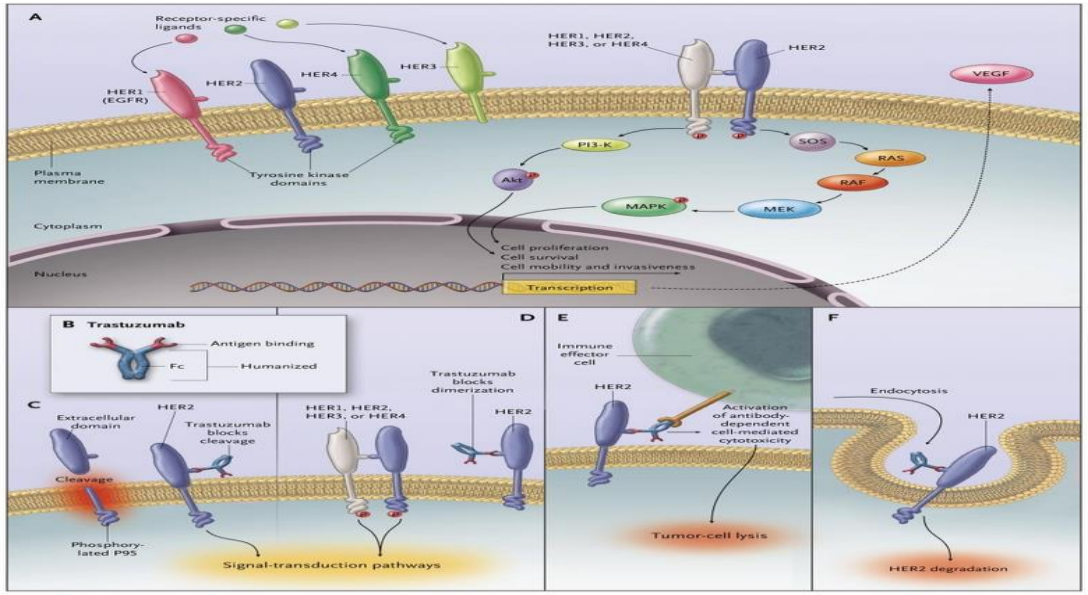
Trends in Breast-Cancer Mortality among Black Women and White Women in the United States, 1970 through 2018.

Age-standardized breast-cancer mortality (deaths per 100,000 women per year) was calculated with the use of SEER*Stat software, version 8.3.9.2, on the basis of the underlying cause of death reported on death certificates. Before 1990, the Census Bureau provided county-level population estimates according to three racial categories: White, Black, and other races. Thus, White race includes Hispanic and non-Hispanic White persons, and Black race includes Hispanic and non-Hispanic Black persons. Adapted and updated from DeSantis et al.[1]

Jatoi et al. *NEJM* 2022, 386;25

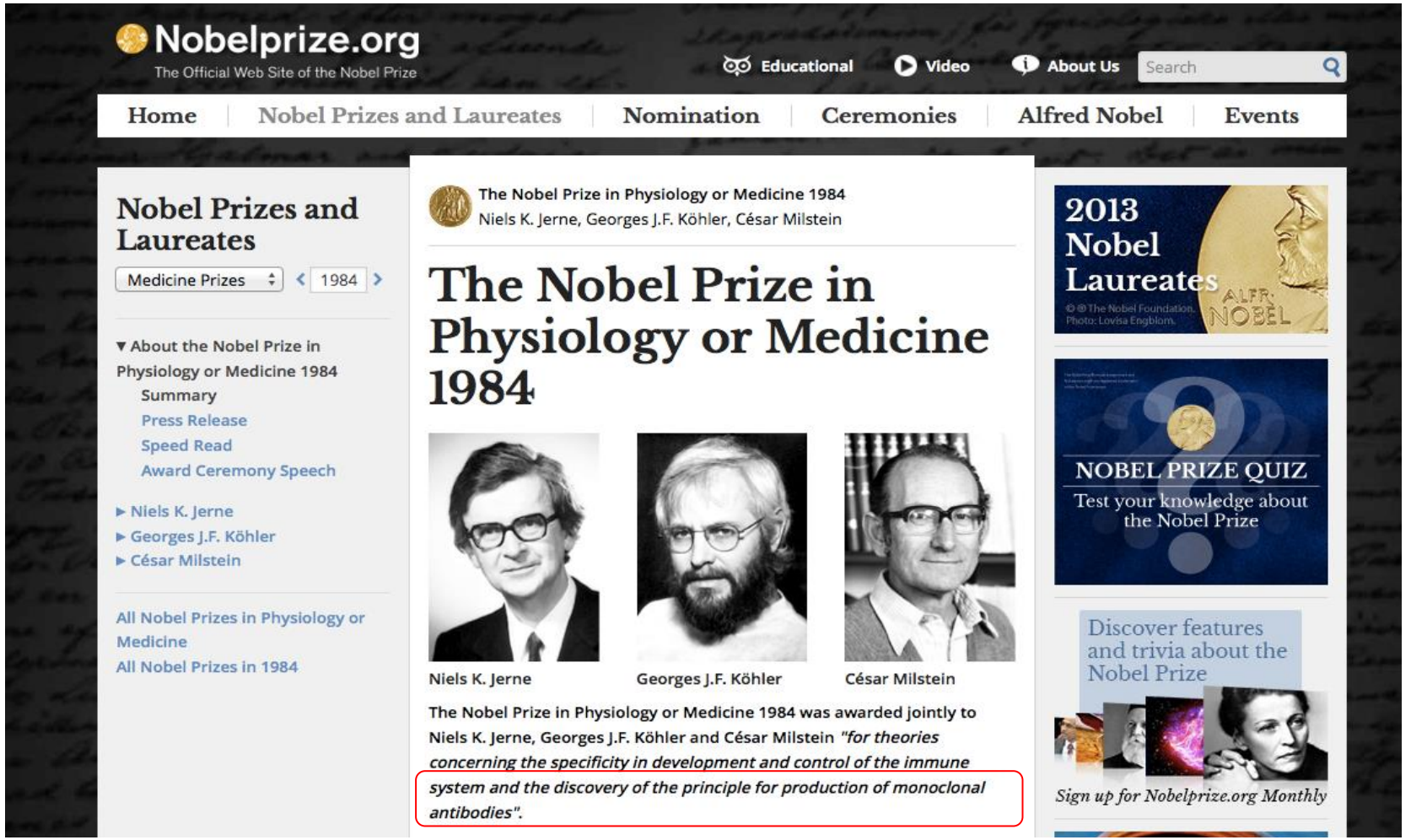
HER2 overexpression

- Tumors that overexpress HER2 are more aggressive and used to be associated with worse outcomes compared to HER2- cancers
- Trastuzumab has altered the natural history of HER2+ BC and addition of trastuzumab to chemotherapy significantly improves DFS and OS in early-stage BC and PFS and OS in MBC.

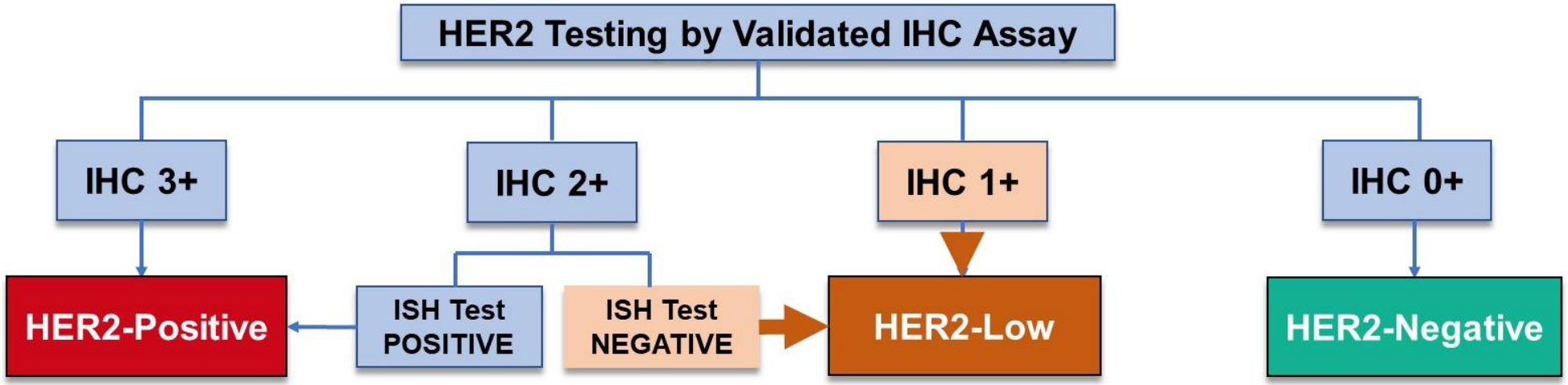


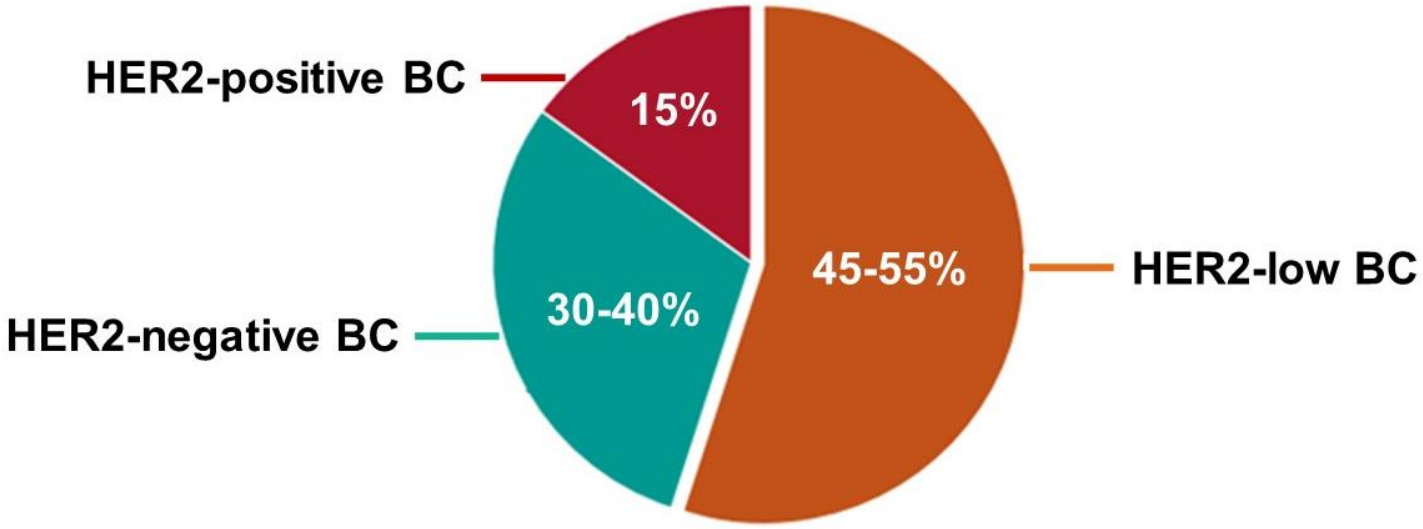
Hudis, NEJM 2007

ANTIBODY DEVELOPMENT



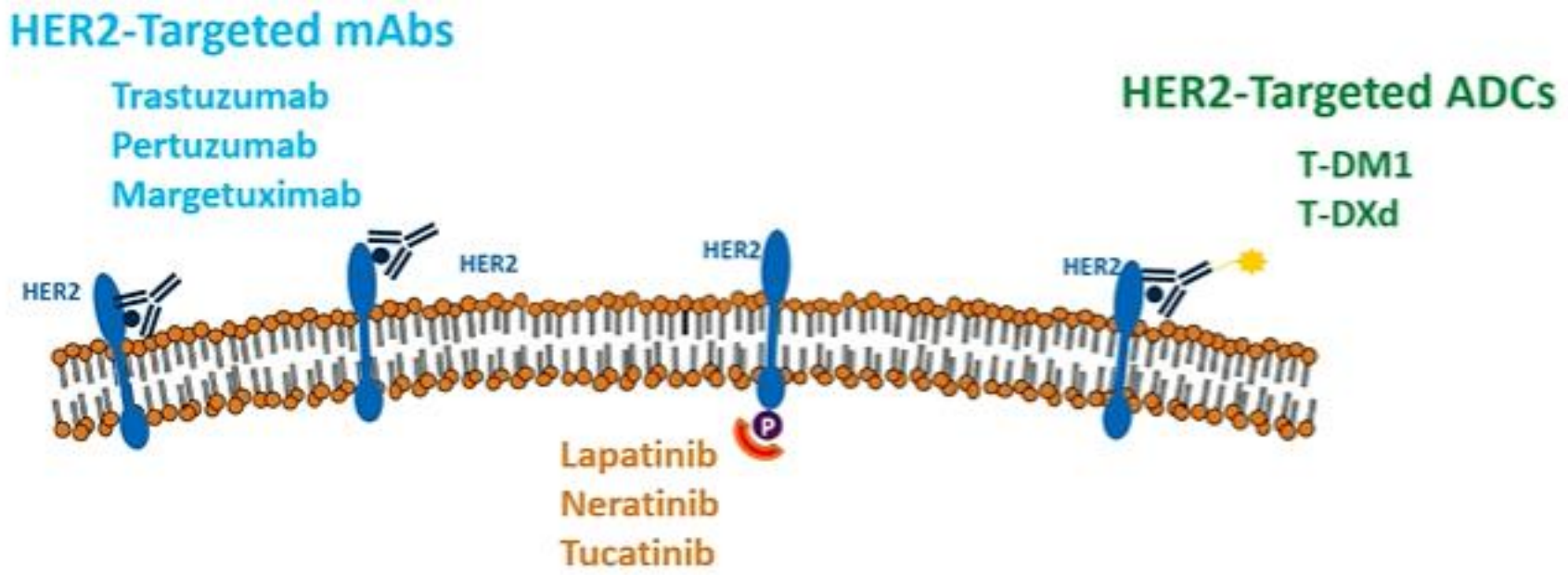
Leavy O: The Birth of monoclonal antibodies, Nature Immunology 17: S13-S13, 2016





Tarantino et al. *JCO*. 2020 38(17)

Targeted Therapies for HER2+ Breast Cancer and FDA Approvals

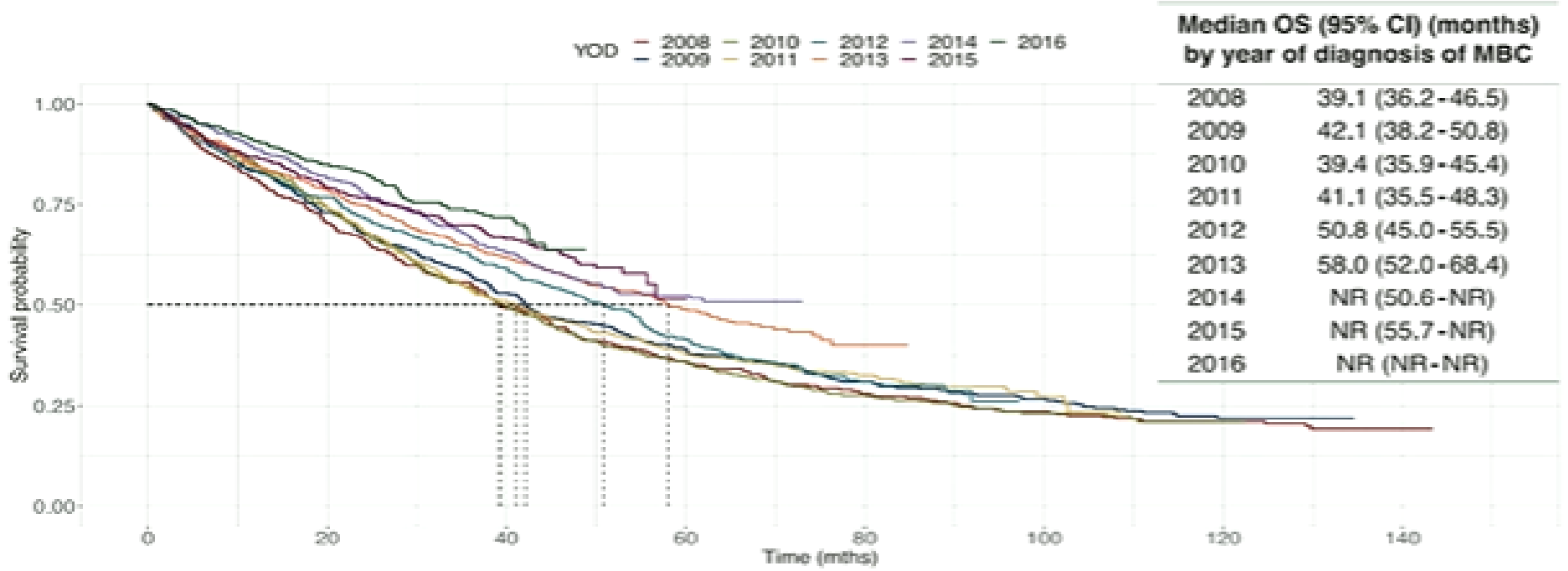


1998	2007-08	2012	2013	2017	2019	2020
Trastuzumab (metastatic)[1]	**Lapatinib** (metastatic)[2]	**Pertuzumab** (metastatic)[3]	**T-DM1** (metastatic)[4]	**Neratinib** (adjuvant)[5]	**T-DM1** (adjuvant)[4]	**Tucatinib** (metastatic)[6]
	Trastuzumab (adjuvant)[1]		**Pertuzumab** (neoadjuvant)[3]	**Pertuzumab** (adjuvant)[3]	**Trastuzumab deruxtecan** (metastatic)[7]	**Neratinib** (metastatic)[5]
						Margetuximab (metastatic)[8]

HER2-Positive MBC

Overall Survival in HER2+ MBC by Year of Diagnosis

ESME-MBC Registry

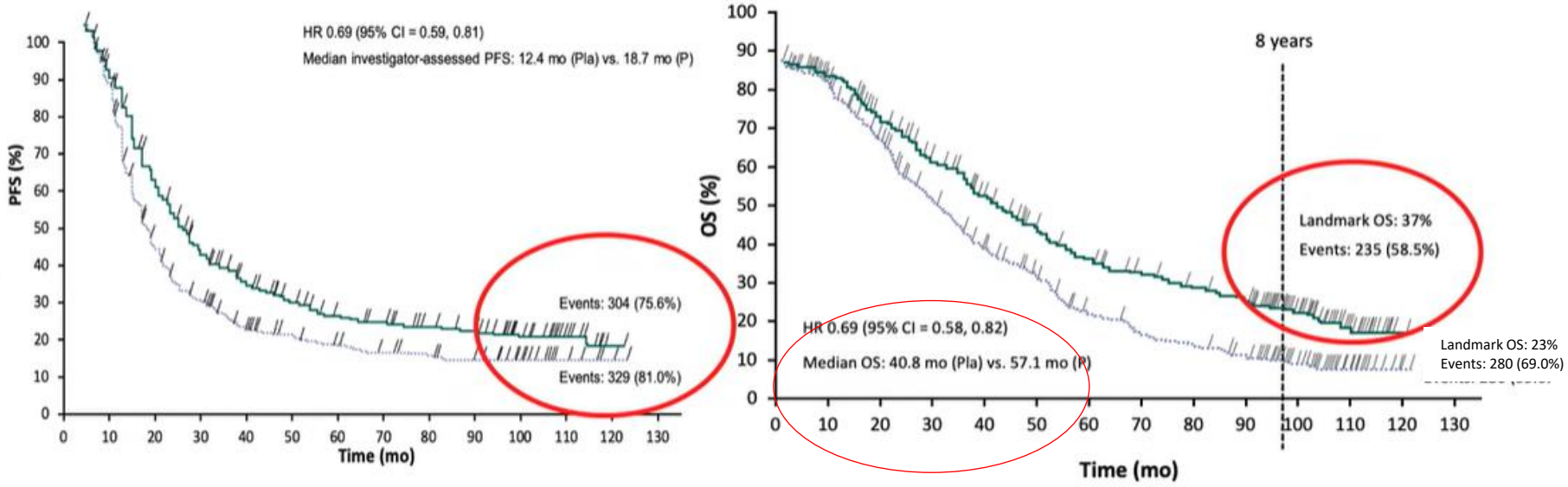


Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	39.1 (36.2-46.5)
2009	42.1 (38.2-50.8)
2010	39.4 (35.9-45.4)
2011	41.1 (35.5-48.3)
2012	50.8 (45.0-55.5)
2013	58.0 (52.0-68.4)
2014	NR (50.6-NR)
2015	NR (55.7-NR)
2016	NR (NR-NR)

Grinda T, et al. *ESMO Open*. 2021;6(3):100114.

HER2 + MBC (CLEOPATRA)

Docetaxel/Trast +/- Pertuzumab in 1L HER2+ MBC



Patients were enrolled from **February 2008 - July 2010.**

8-year landmark OS of 37%

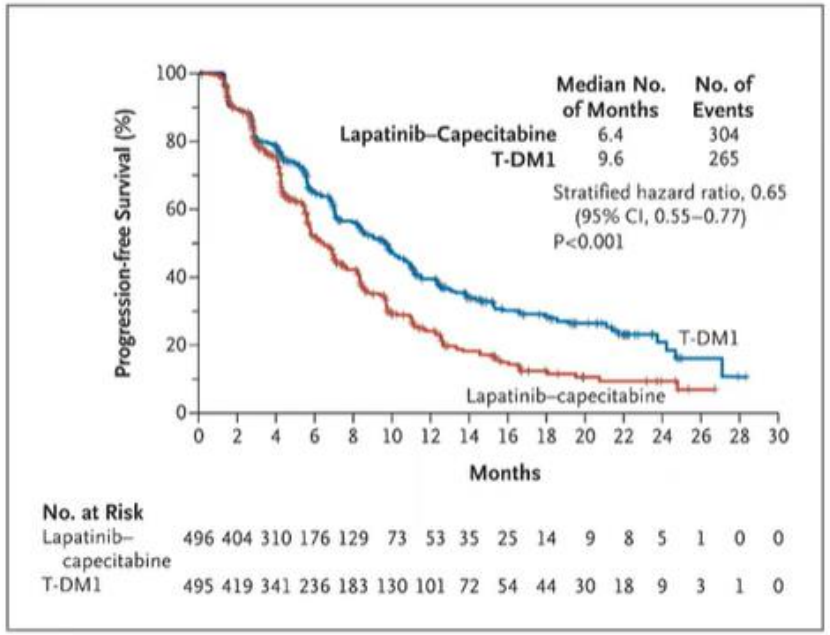
Median PFS: 18 mo

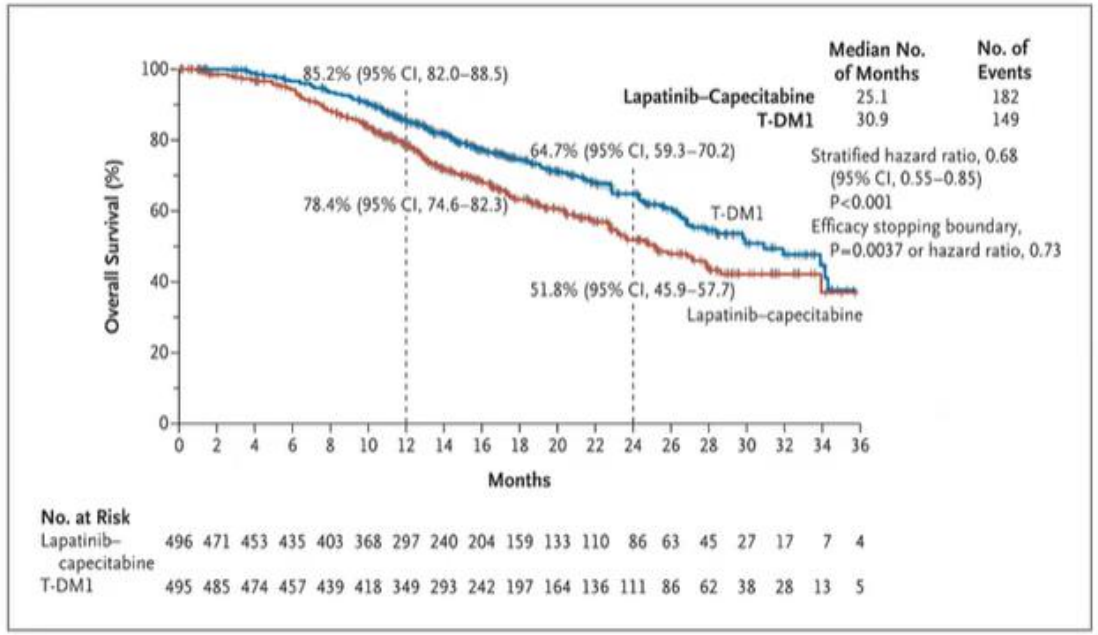
Median OS: 57 mo

Swain S, et al. Presented at: ASCO Annual Meeting; 2019. Swain S, et al. *Lancet Oncol*. 2020;21(4):519-530.

EMILIA Study

TDM1 vs Lapatinib-Capecitabine in 2L HER2+ MBC





Patients were enrolled from **February 2009 - October 2011**

Median OS: 25.1 vs 30.9 mo

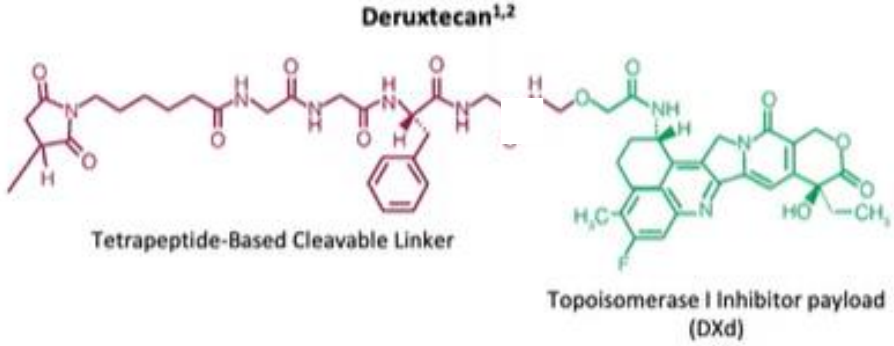
T-DM1 = trastuzumab emtansine.

Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791.

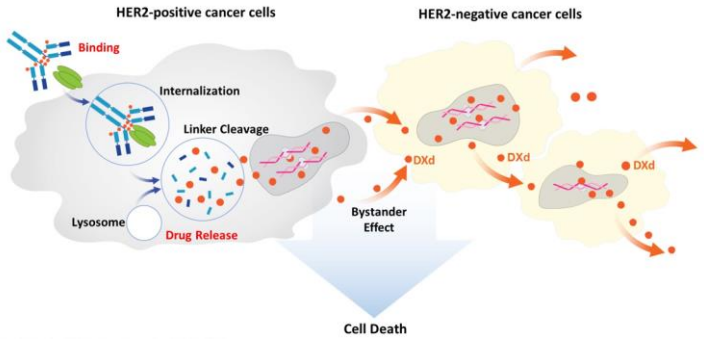
Trastuzumab Deruxtecan

Trastuzumab deruxtecan is an ADC composed of 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



T-DXd Mechanism of Action



Payload: topoisomerase I inhibitor (10 times more potent than SN38)

High drug to antibody ratio ≈ 8

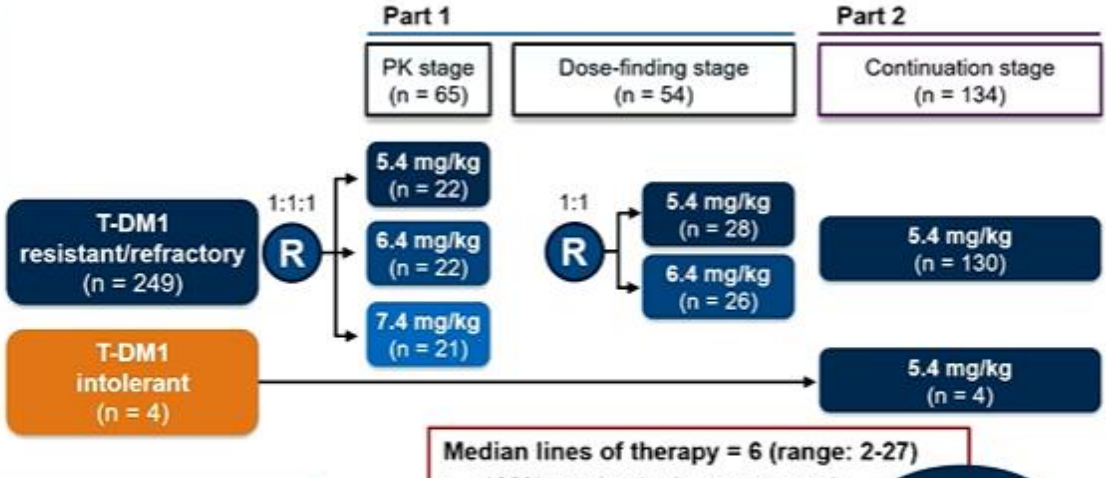
Membrane-permeable payload

Half-life of intact ADC is 6 days

Nakada T, et al. *Chem Pham Bull* (Tokyo). 2019;67(3):173-185. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046. Mosele, ESMO Breast 2022

DESTINY-Breast01: Phase 2 Study of T-DXd in HER2-Positive MBC

- ≥18 years of age
- Unresectable and/or metastatic BC
- ***HER2* positive** (centrally confirmed on archival tissue)
- **Prior T-DM1**
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed



- **Primary endpoints:** confirmed ORR by independent central imaging facility review per RECIST v1.1
- **Secondary endpoints:** investigator-assessed ORR, DCR, DOR, CBR, PFS, OS, PK, and safety

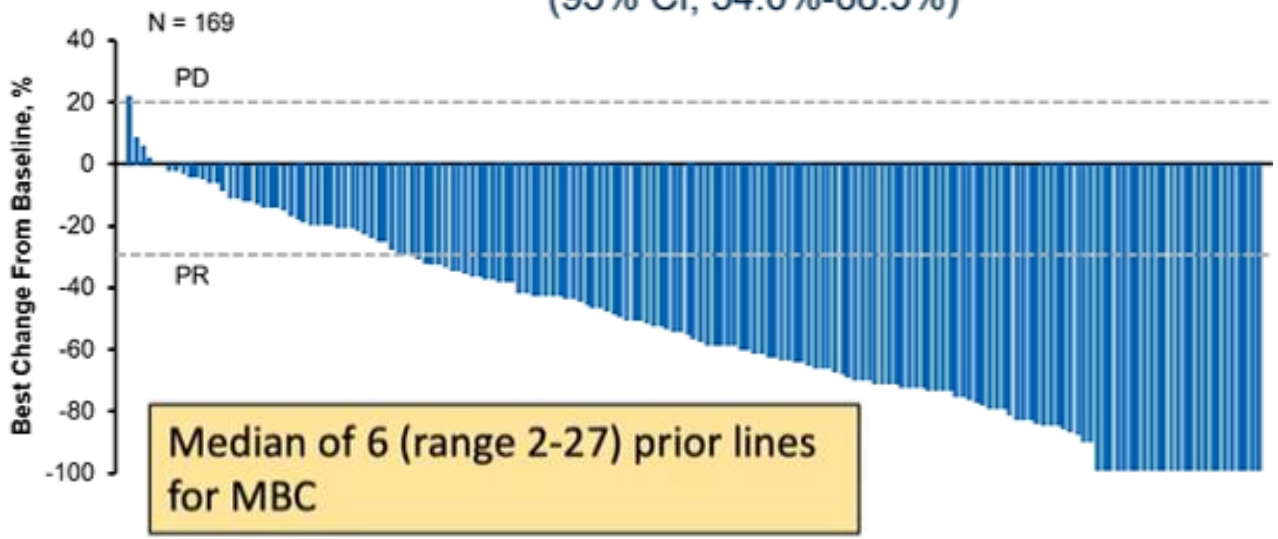
Median lines of therapy = 6 (range: 2-27)

- 100% received prior trastuzumab
- 100% received prior T-DM1
- 66% received prior pertuzumab
- 54% received other HER2 therapies

184 patients

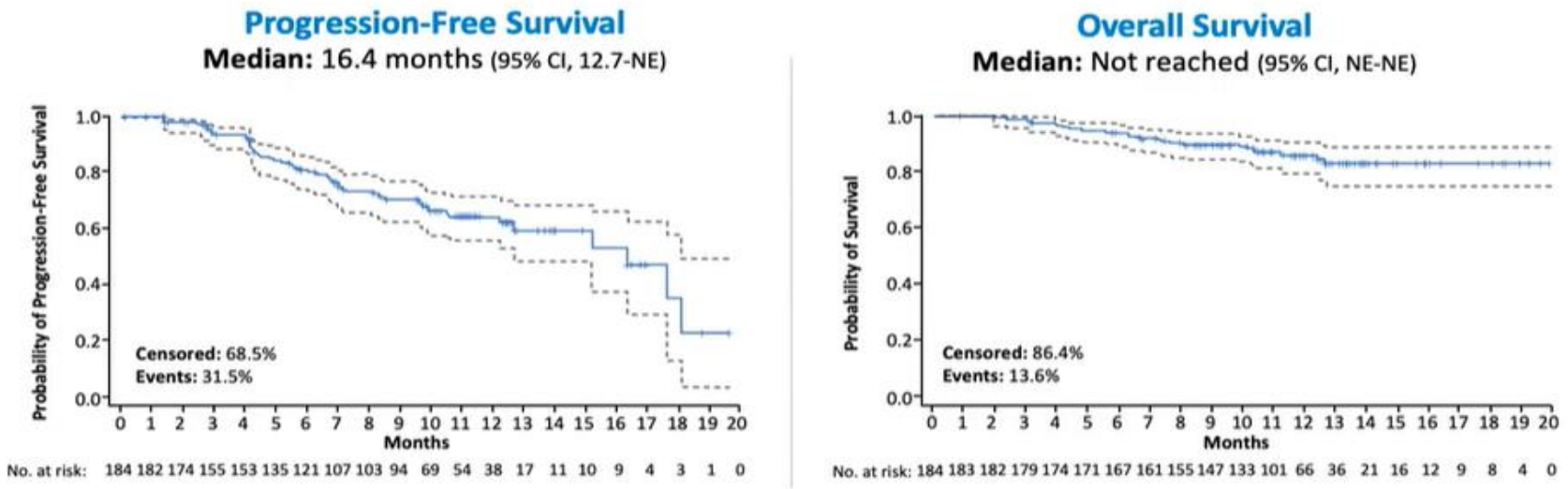
Updated ORR Results with 20.5 Months Follow-Up

Confirmed Overall Response Rate was 61.4%
(95% CI, 54.0%-68.5%)



ILD = interstitial lung disease; CBR = clinical-benefit rate; PK = pharmacokinetics.
Modi S, et al. *N Engl J Med*. 2020;382(7):610-621.

DESTINY-Breast01:
Trastuzumab Deruxtecan for 3L+ HER2+ MBC



- Median follow-up, 11.1 months (range, 0.7-19.9 months)
- Median PFS in the 24 patients with brain metastases was 18.1 months (95% CI, 6.7-18.1 months)

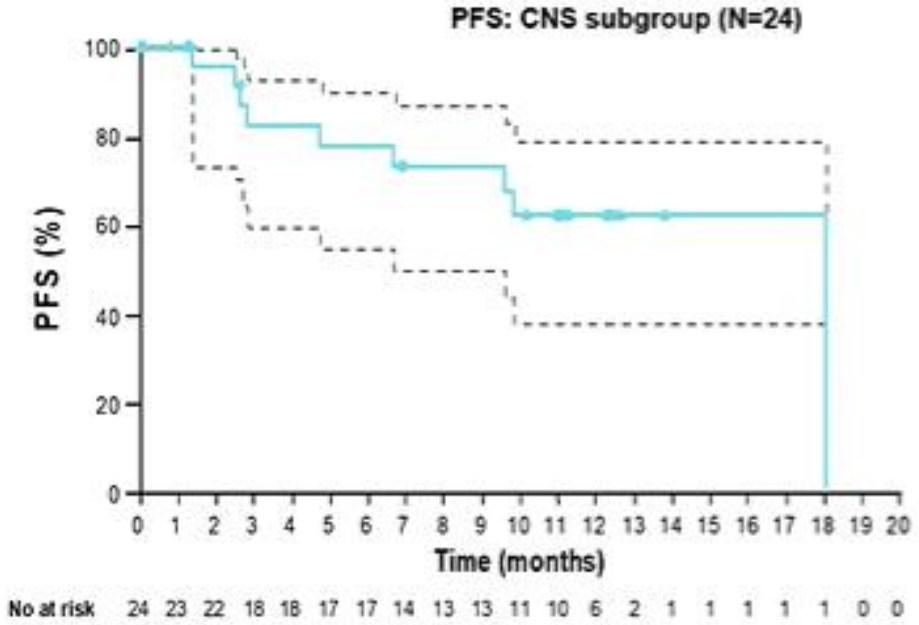
Patients who received T-DXd 5.4 mg/kg.
CI, confidence interval; NE, not estimable.

Patients were enrolled from **October 2017 – September 2018**

Additional 9.4 mo F/U showed PFS 19.4 mo and median OS was 24.6 mo

Median OS update at ESMO 2021: 29.1 months in exploratory analysis with 31.1 months of F/U.
Modi S, et al. *N Engl J Med*. 2020;382(7):610-621.

T-DXd Showed Similar Efficacy in Patients with a History of CNS Metastases at Baseline to the Overall Population



	CNS subgroup (N=24)	All patients (N=184)
Confirmed ORR by ICR, n (%) (95% CI)	**14 (58.3)** (36.6–77.9)	**112 (60.9)** (53.4–68.0)
DCR, n (%)	22 (91.7)	179 (97.3)
TTR, median, months (95% CI)	2.8 (1.3–4.1)	1.6 (1.4–2.6)
DOR (CR or PR), median, months (95% CI)	16.9 (5.7–16.9)	14.8 (13.8–16.9)
PFS, median, months (95% CI)	**18.1** (6.7–18.1)	**16.4** (12.7–NE)

Median PFS in patients with brain metastases: T-DXd: 15 mo
SOC arm: 3 mo

Drug-Related ILD/Pneumonitis

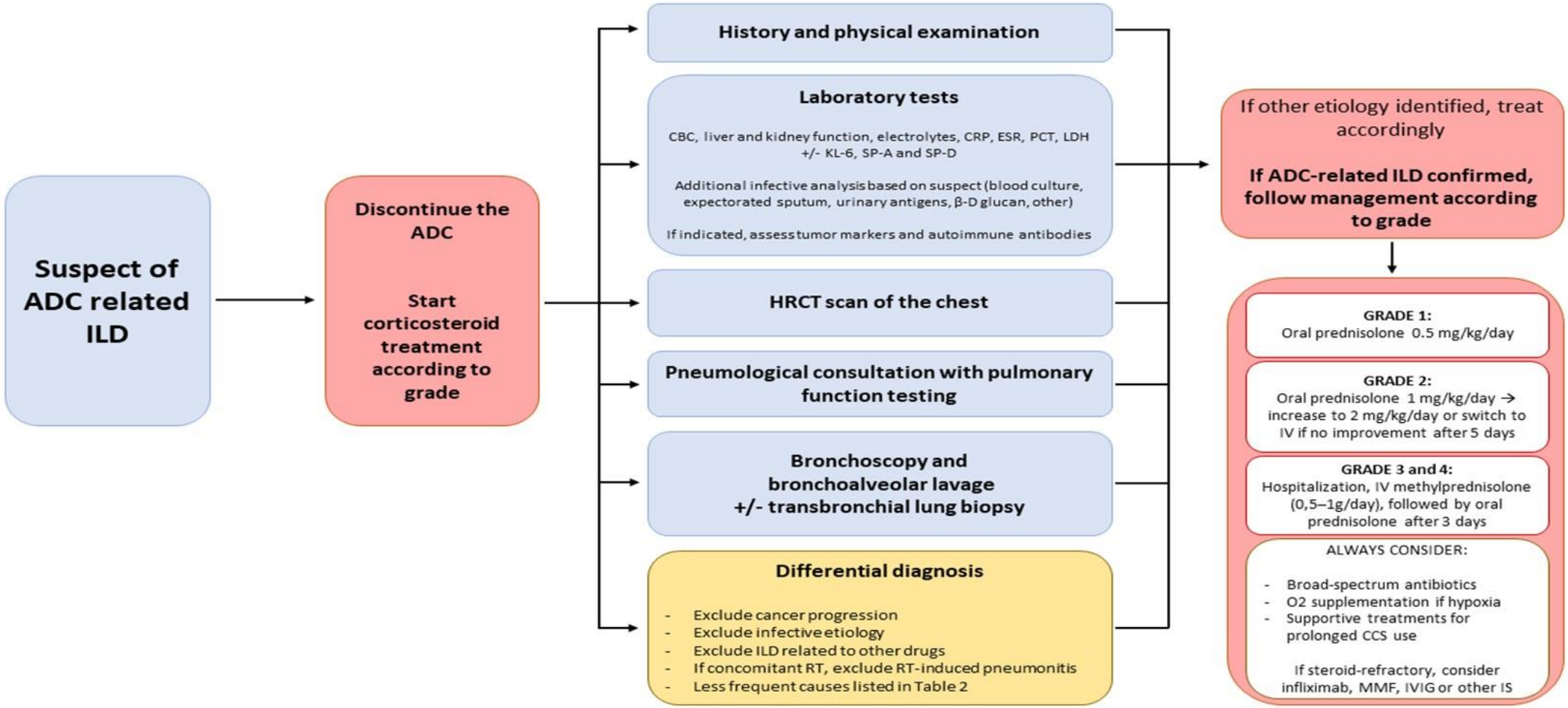
Interstitial lung disease, n (%)	T-DXd 5.4 mg/kg (N=184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/ Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	**28 (15.2)**

[a]As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.

- Median time to onset of ILD was 27.6 weeks
- Requires awareness via monitoring, dose interruptions/modification, and early institution of steroids
- Majority of cases occur within 12-14 months of therapy; no cumulative risk

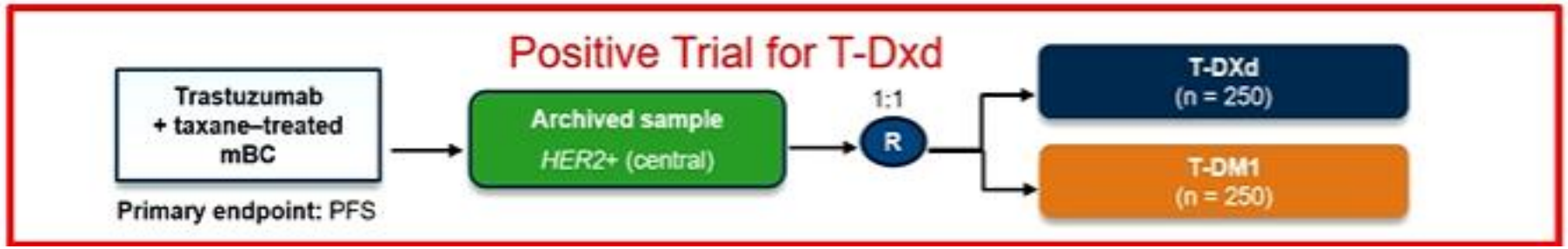
Jerusalem G, et al. Presented at: ESMO Breast Cancer Virtual Meeting; 2020. Hurvitz S, et al. SABCS2021, Modi S, et al. Presented at: SABCS; 2020.

Diagnostic Algorithm for managing ILD



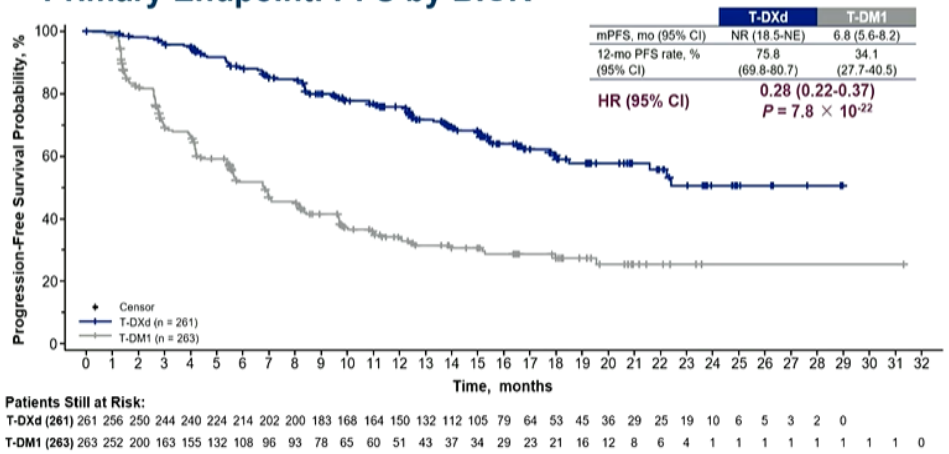
Tarantino P, et al. JAMA Oncol 2021

DESTINY-Breast03 – T-DXd in 2nd line



Presidential presentation on 9/18 at ESMO 2021 by Dr. Cortes: PFS HR: 0.28 for T-DXd

Primary Endpoint: PFS by BICR

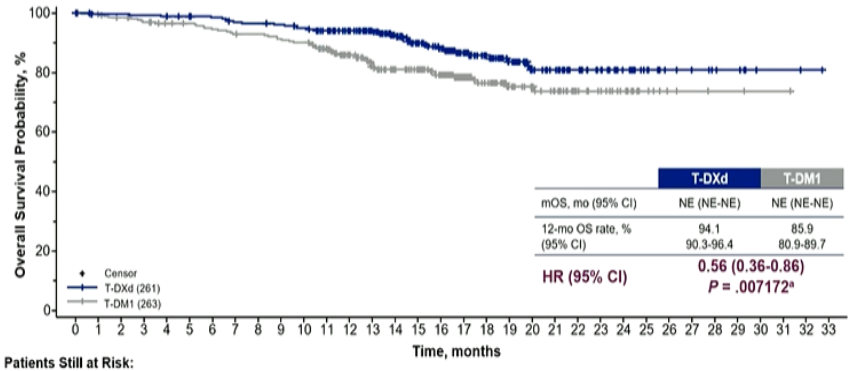


	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

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	0

Key Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 (90.3-96.4)	85.9 (80.9-89.7)
HR (95% CI)	0.56 (0.36-0.86)	
	$P = .007172^a$	

Patients Still at Risk:

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a] $P = .007172$, but does not cross pre-specified boundary of $P < .000265$

- **Median treatment duration was 14.3 months (range, 0.7-29.8) for T-DXd and 6.9 months (range, 0.7-25.1) for T-DM1**
- The most common TEAE associated with treatment discontinuation for T-DXd was ILD/pneumonitis[a] (8.2%) and for T-DM1 was thrombocytopenia[b] (2.7%)

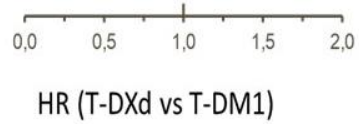
TEAE = treatment-emergent AE.

Cortes J, et al. Presented at: ESMO Congress; 2021, *NEJM* 2022 March 24; 386 (12):1143-1154

DESTINY-Breast03 – T-DXd in 2nd line

	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

		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)



Cortes J, et al. Presented at: ESMO Congress; 2021, *NEJM* 2022 March 24; 386 (12):1143-1154

Tucatinib – HER2CLIMB

Key Eligibility Criteria
- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline

*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

R* (2:1)

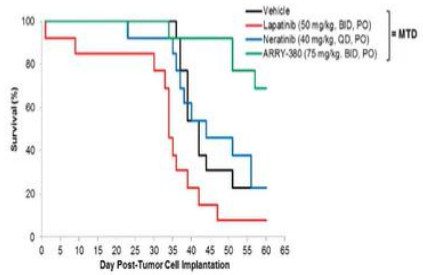
N=410: **Tucatinib** 300 mg PO BID + **Trastuzumab** 6 mg/kg Q3W, loading dose 8 mg/kg C1D1 + **Capecitabine** 1000 mg/m² PO BID Days 1-14; *21-day cycle*

N=202: **Placebo** + **Trastuzumab** 6 mg/kg Q3W, loading dose 8 mg/kg C1D1 + **Capecitabine** 1000 mg/m² PO BID Days 1-14; *21-day cycle*

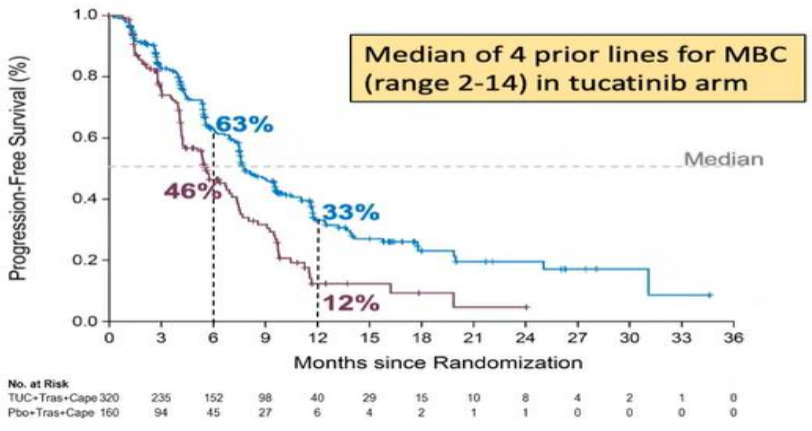
- Oral, HER2-selective, tyrosine kinase inhibitor
- Preclinical activity in HER2+ breast cancer models, including intracranial models
- Extracranial and intracranial a vity observed in phase 1 program

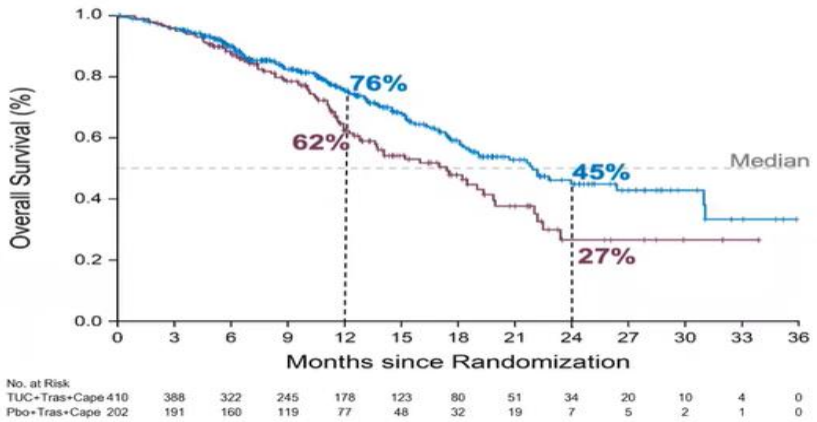
Cellular Selectivity Data

Compound	HER2 IC_{50} (nM)	EGFR IC_{50} (nM)	HER2 IC_{50} (nM) 50% Human Serum
ARRY-380	8	4000	67
Neratinib	7	8	39
Lapatinib	49	31	810



Patients with or without brain mets
PFS HR 0.54; medians 5.6 vs 7.8 months; p <0.001
OS HR 0.66; medians 17.4 months vs 21.9 months; p=0.005





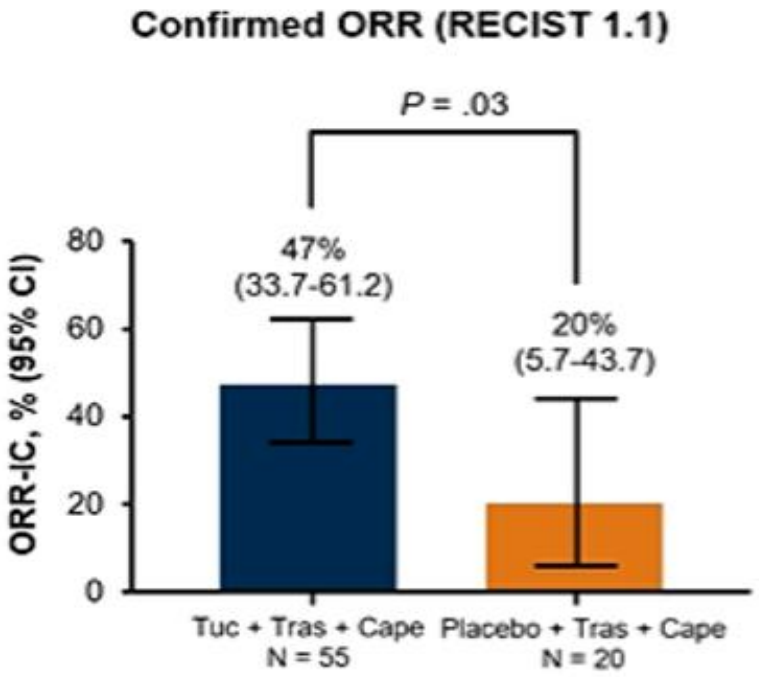
Patients were enrolled from **February 2016 – May 2019**

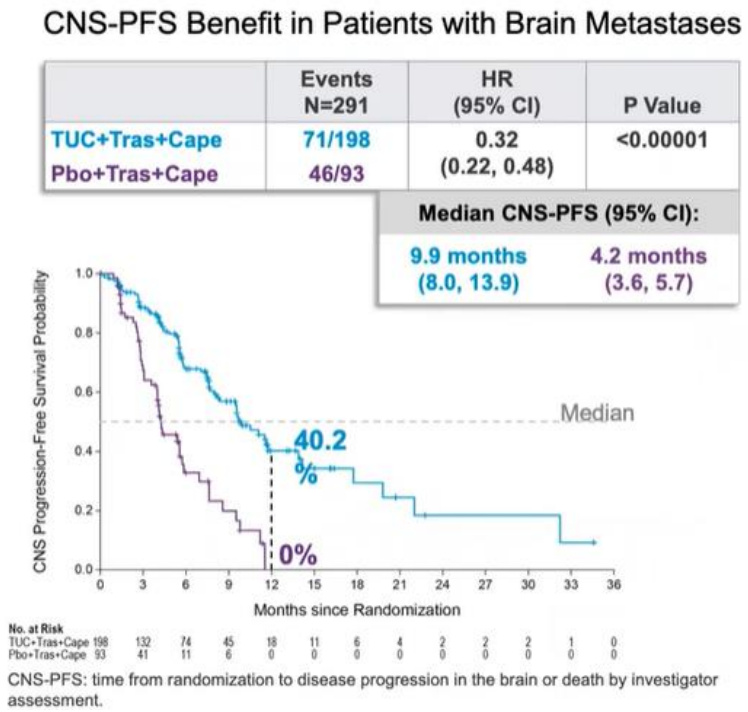
21.9 months	17.4 months
(18.3, 31.0)	(13.6, 19.9)

EGFR = estimated glomerular filtration rate.

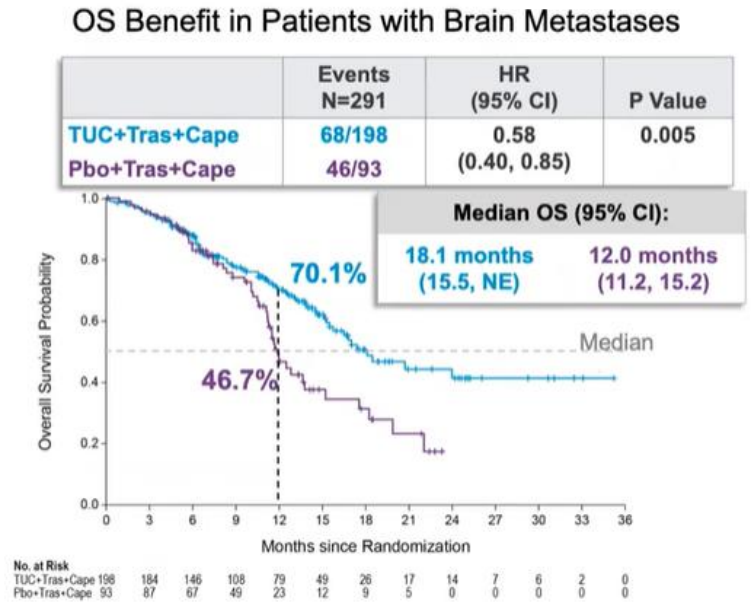
ClinicalTrials.gov. Accessed September 21, 2021. https://clinicaltrials.gov/ct2/show/NCT02614794. Pheneger T, et al. Presented at: AACR Annual Meeting; 2009. Moulder SL, et al. *Clin Cancer Res*. 2017;23(14):3529-3536. Murthy R, et al. *Lancet Oncol*. 2018;19(7):880-888. Metzger Filho O, et al. *Ann Oncol*. 2020;31(9):1231-1239. Murthy RK, et al. *N Engl J Med*. 2020;382(7):597-609.

CNS Metastasis – HER2CLIMB Improves ORR, CNS PFS, and OS





CNS-PFS: time from randomization to disease progression in the brain or death by investigator assessment.

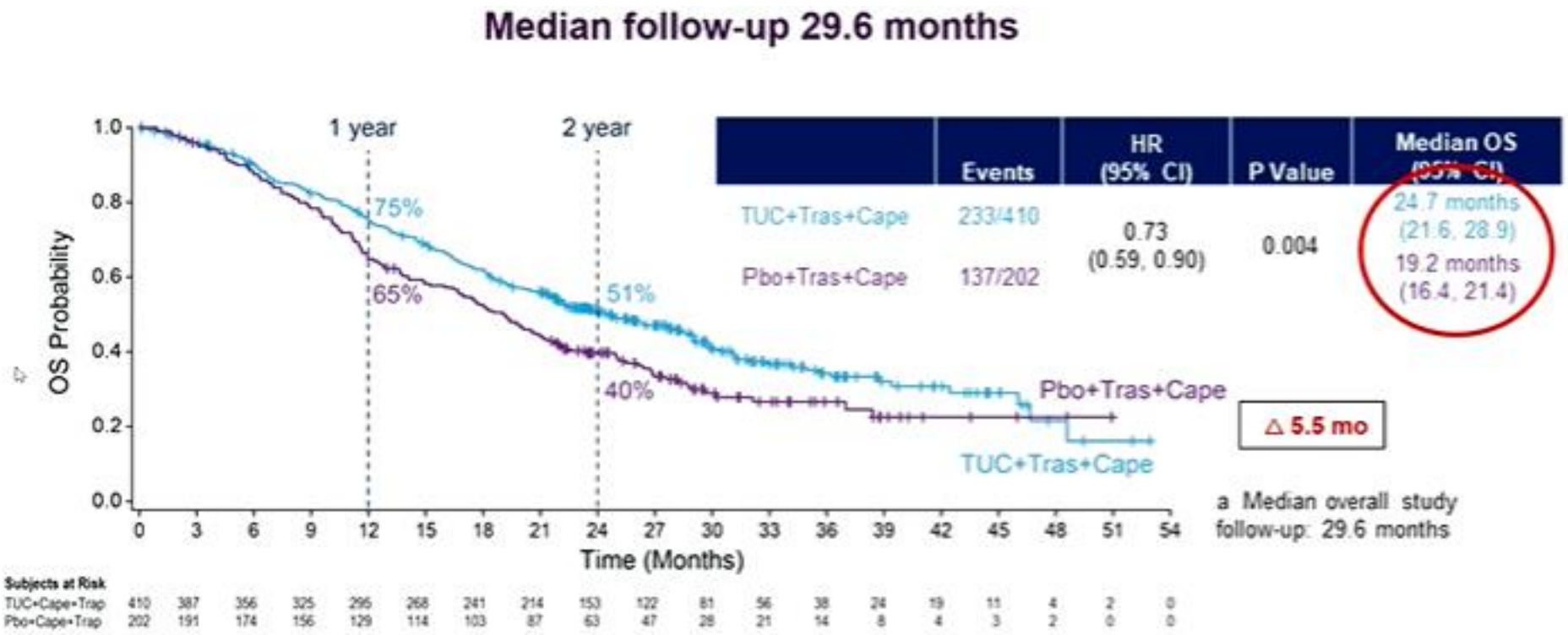


HR computed from Cox proportional hazards model using stratification factors (ECOG PS: 0/1, and region of world: North America/rest of world) at randomization.

TUC = tucatinib.

Von Minckwitz G, et al. *N Engl J Med*. 2019;380(7):617-628. Pestalozzi BC, et al. *Lancet Oncol*. 2013;14(3):244-248. Lin NU, et al. *J Clin Oncol*. 2020;38(23):2610-2619.

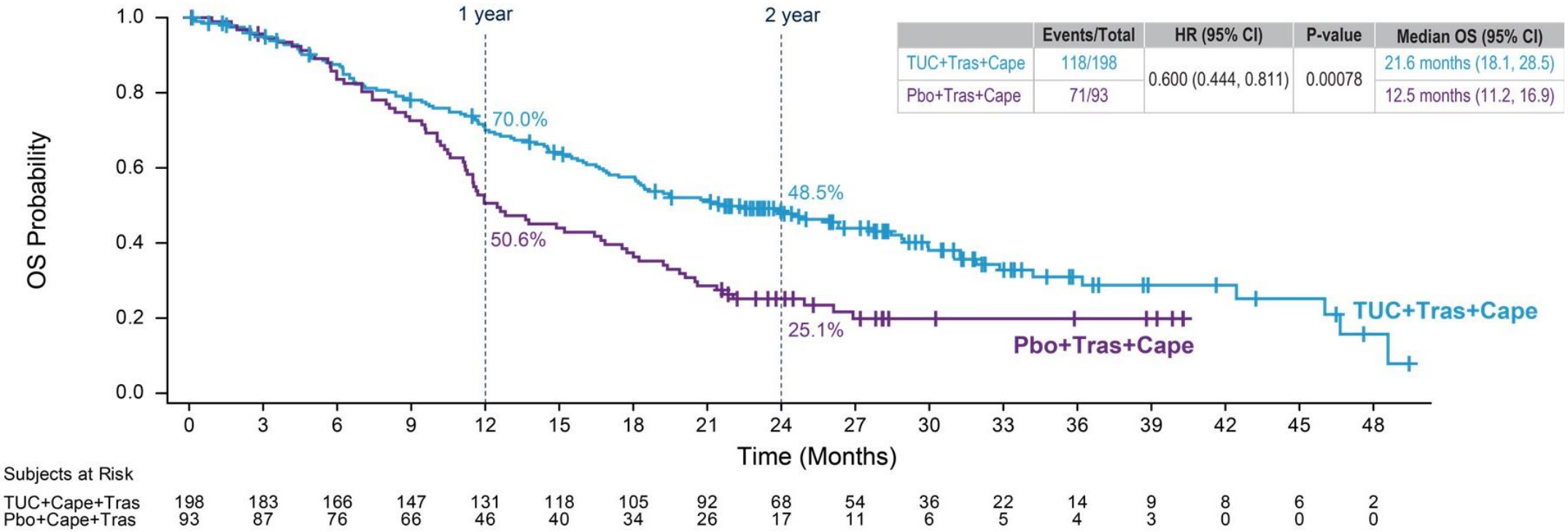
HER2CLIMB: Updated Overall Survival



- OS benefit with tucatinib was maintained with longer follow-up, with a 5.5 month improvement in median OS in the tucatinib arm compared to the placebo arm.
- Sensitivity analyses accounting for cross-over showed consistent results with ITT analysis

Curigliano G, et al. Presented at: ASCO Annual Meeting; 2021.

HER2CLIMB: OS Benefit in Patients with BCBM

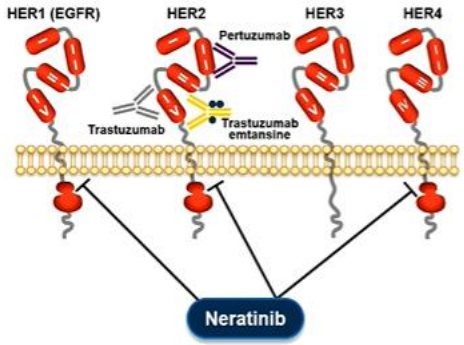


	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	118/198	0.600 (0.444, 0.811)	0.00078	21.6 months (18.1, 28.5)
Pbo+Tras+Cape	71/93			12.5 months (11.2, 16.9)

9.1 month absolute improvement in OS associated with tucatinib

Lin et al, SABCS 2021

Neratinib: A Pan-HER Kinase Inhibitor



NALA: Phase 3 Trial of Neratinib for HER2+ MBC

Inclusion criteria
- MBC
- Centrally confirmed HER2+ disease
- ≥ 2 lines of HER-directed therapy for MBC
- Asymptomatic and stable brain metastases permitted

Prior Pertuzumab and TDM1 not required

R 1:1 n = 621

- Neratinib 240 mg/d + Capecitabine 1,500 mg/m² 14/21 days Loperamide (cycle1)*
- Lapatinib 1,250 mg/d + Capecitabine 2,000 mg/m² 14/21 days

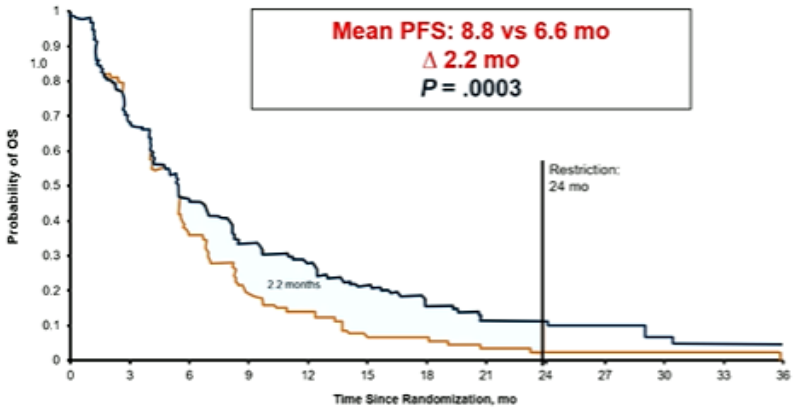
No endocrine therapy permitted

→ Follow-up (survival)

Endpoints
- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DOR, CBR, intervention for CNS metastases, safety, health outcomes

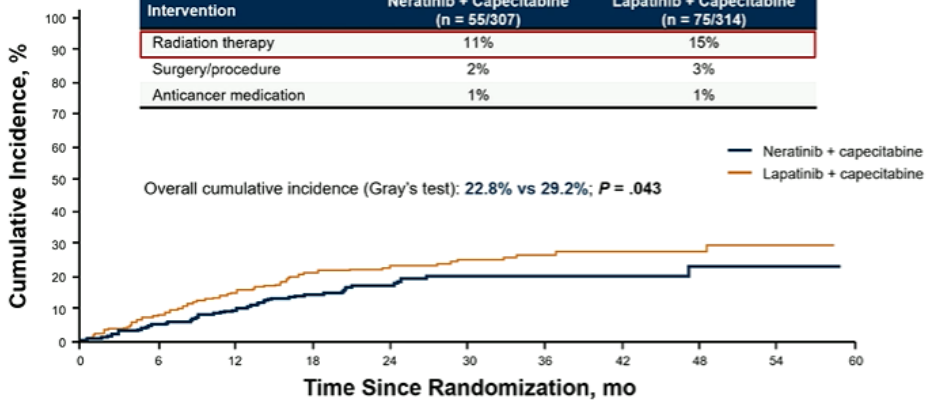
NALA Trial: Centrally Confirmed Mean PFS

Primary Endpoint



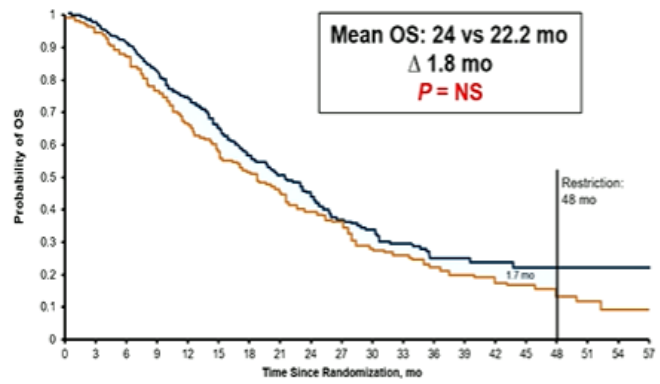
NALA Trial: CNS Benefits in favor of Neratinib

Intervention	Neratinib + Capecitabine (n = 55/307)	Lapatinib + Capecitabine (n = 75/314)
Radiation therapy	11%	15%
Surgery/procedure	2%	3%
Anticancer medication	1%	1%



NALA Trial: No Difference in OS

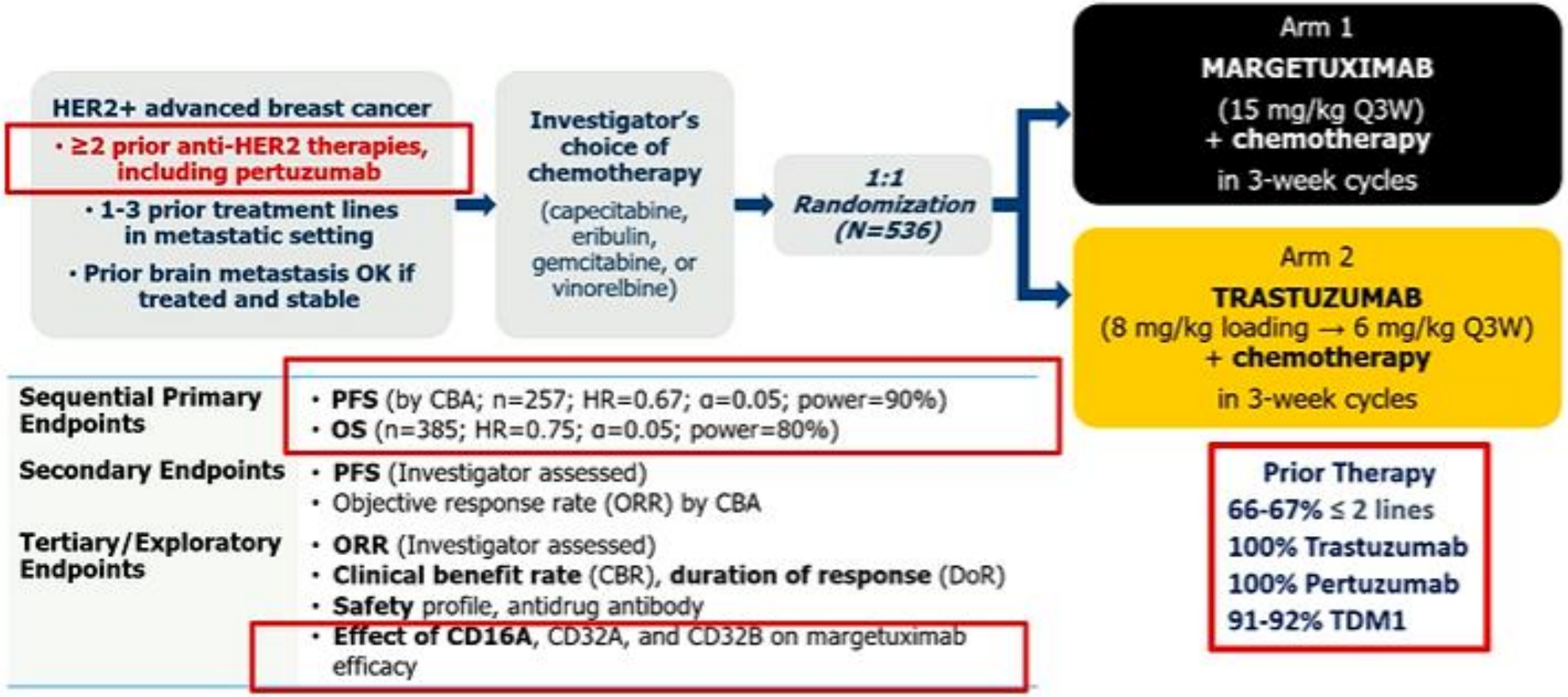
Primary Endpoint



Baselga J, et al. *Crit Rev Oncol Hematol*. 2017;119:113-122. Kim JY, et al. *Int J Cancer*. 2019;145(6):1669-1678. Kunte S, et al. *Cancer*. 2020;126(19):4278-4288. Xuhong JC, et al. *Am J Cancer Res*. 2019;9(10):2103-2119. Saura C, et al. *J Clin Oncol*. 2020;38(27):3138-3149.

Margetuximab: A Novel HER2 mAB with a Modified Fc Domain

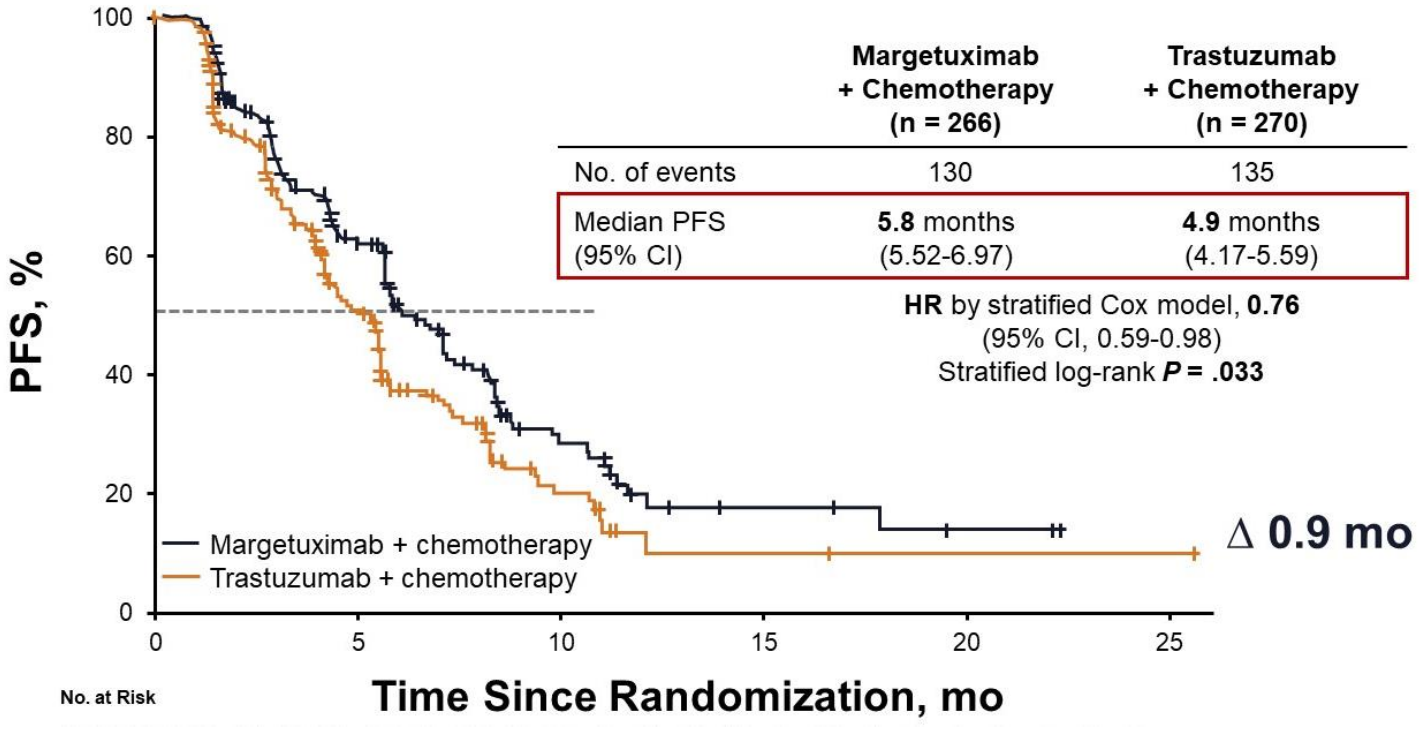
SOPHIA Study: Randomized Phase 3 Design



CBA = central blinded analysis.
Rugo H, et al. Presented at: SABCS; 2019.

Phase 3 SOPHIA Trial: Primary Endpoint PFS

24% Risk Reduction of Disease Progression



	Margetuximab + Chemotherapy (n = 266)	Trastuzumab + Chemotherapy (n = 270)
No. of events	130	135
Median PFS (95% CI)	**5.8** months (5.52-6.97)	**4.9** months (4.17-5.59)

HR by stratified Cox model, **0.76** (95% CI, 0.59-0.98)
Stratified log-rank ***P*** **= .033**

Δ 0.9 mo

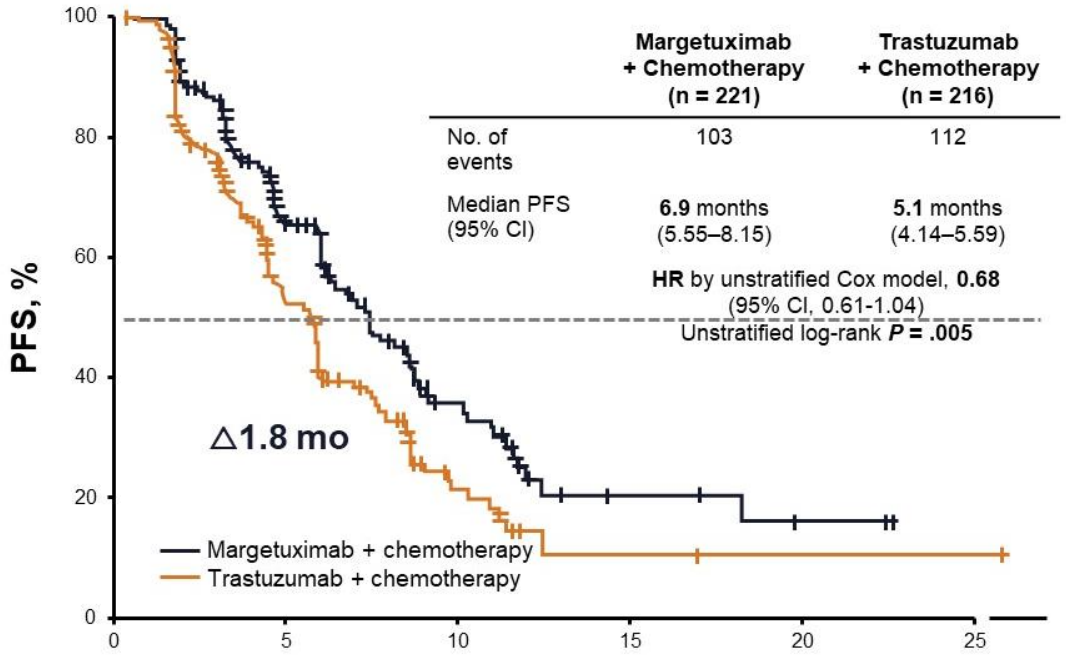
Approved by the FDA in December 2020 for patients with HER2+ MBC that have received two or more prior HER2-directed regimens

Rugo H et al. *JAMA Oncol* 2021 Apr 1;7(4)573-584

SOPHIA trial: exploratory analysis by genotype

CD16A FF or FV, n = 437 of 506 Genotyped (86%)

PFS

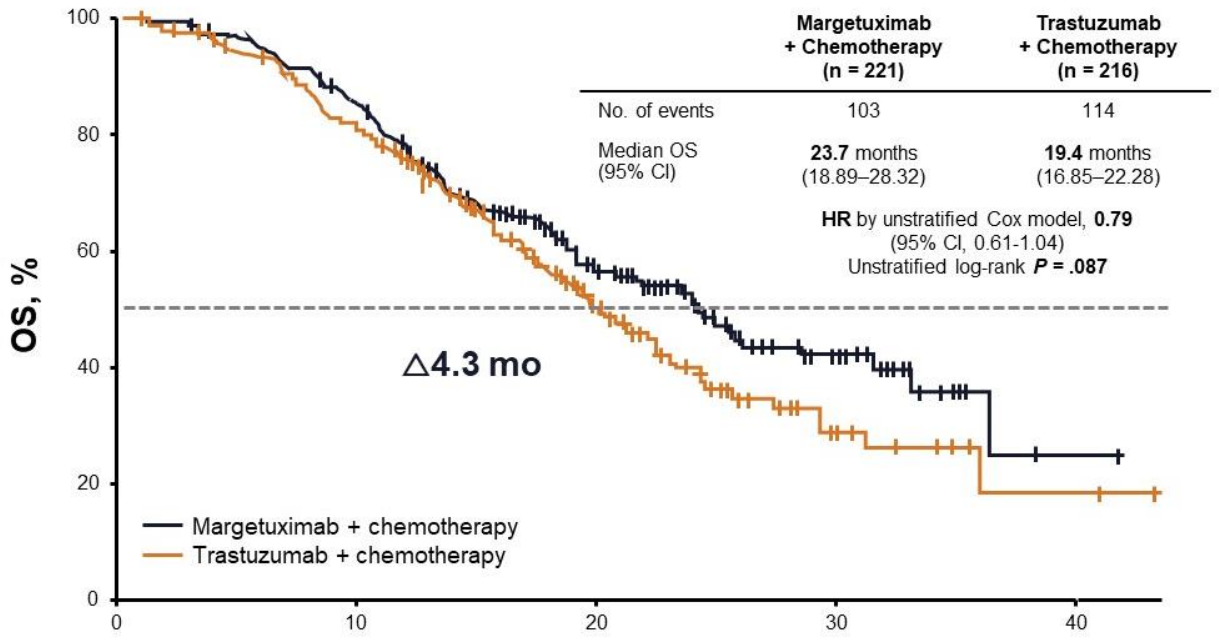


	Margetuximab + Chemotherapy (n = 221)	Trastuzumab + Chemotherapy (n = 216)
No. of events	103	112
Median PFS (95% CI)	**6.9** months (5.55–8.15)	**5.1** months (4.14–5.59)

HR by unstratified Cox model, **0.68** (95% CI, 0.61-1.04)
Unstratified log-rank ***P* = .005**

No. at Risk											
Margetuximab	221	157	84	42	21	8	6	4	2	0	
Trastuzumab	216	129	62	30	11	2	2	1	1	1	1

OS



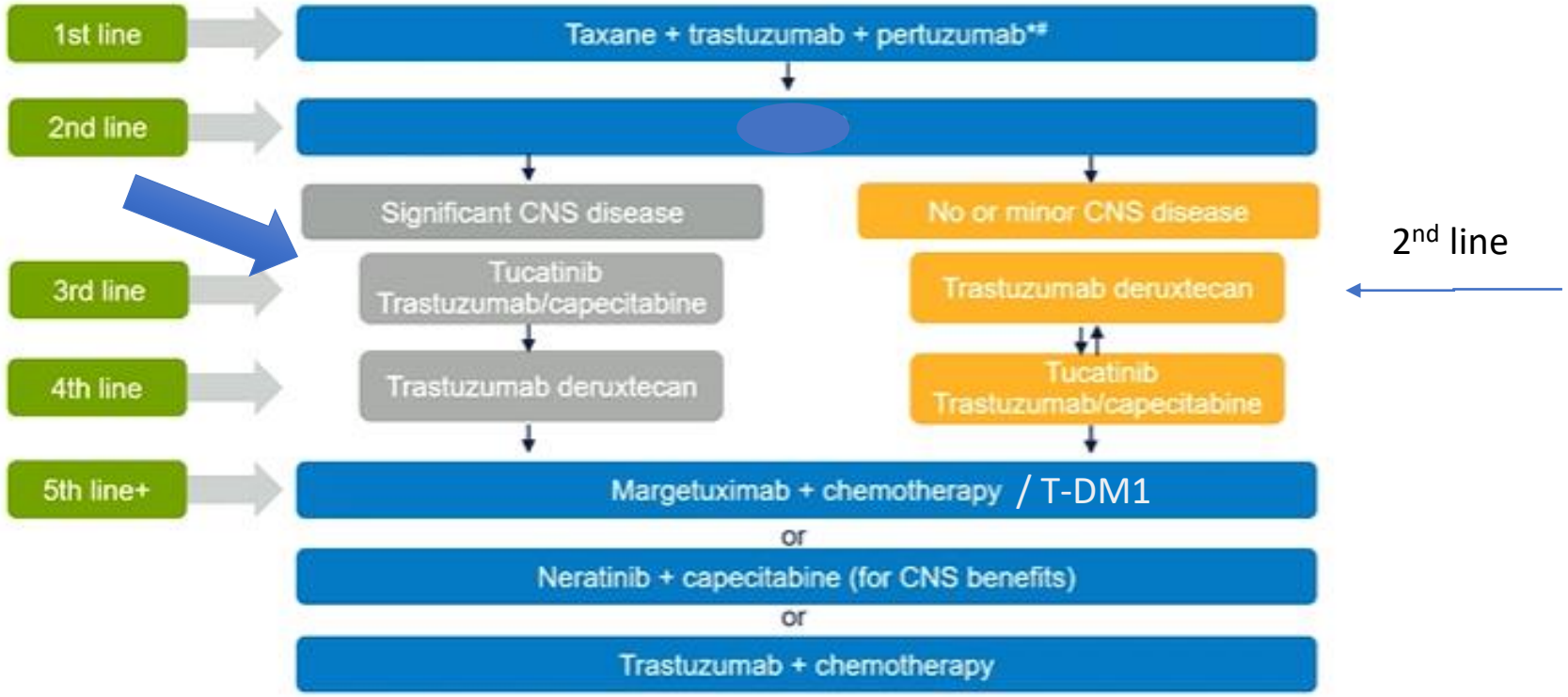
	Margetuximab + Chemotherapy (n = 221)	Trastuzumab + Chemotherapy (n = 216)
No. of events	103	114
Median OS (95% CI)	**23.7** months (18.89–28.32)	**19.4** months (16.85–22.28)

HR by unstratified Cox model, **0.79** (95% CI, 0.61-1.04)
Unstratified log-rank ***P* = .087**

No. at Risk																							
Margetuximab	221	219	212	204	196	181	157	135	111	91	68	55	42	31	27	19	13	8	2	1	1	0	
Trastuzumab	216	210	201	192	176	165	145	123	98	81	57	43	30	21	16	11	9	6	2	2	2	1	0

Rugo H et al. *JAMA Oncol* 2021 Apr 1;7(4)573-584

2022 Approach to Therapy for Metastatic HER2+ BC



2nd line

*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

Tucatinib + Trastuzumab + Capecitabine	Trastuzumab deruxtecan	Neratinib + Capecitabine	Margetuximab + chemotherapy
+ OS Advantage	+ High probability of tumor response	+ All oral regimen	+ Novel immune mechanism
+ CNS activity	+ Durable tumor control	+ CNS activity	+ Favorable safety
+ Effective post-TDM1	+ Active in HER2 heterogeneity	- GI Toxicity	- Modest activity
- diarrhea	- Requires Pulmonary Monitoring	- No OS	- No OS yet
		- Activity post Tucatinib & cape?	- Patient selection?

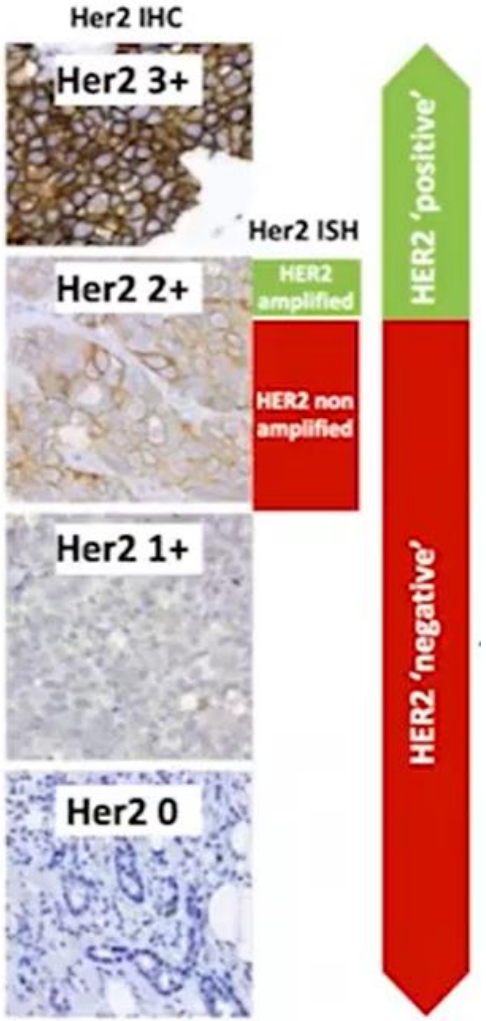
GI = gastrointestinal.

Modi S, et al. Presented at: ESMO; 2021.

Trastuzumab Deruxtecan in Previously Treated HER2-low Advanced Breast Cancer

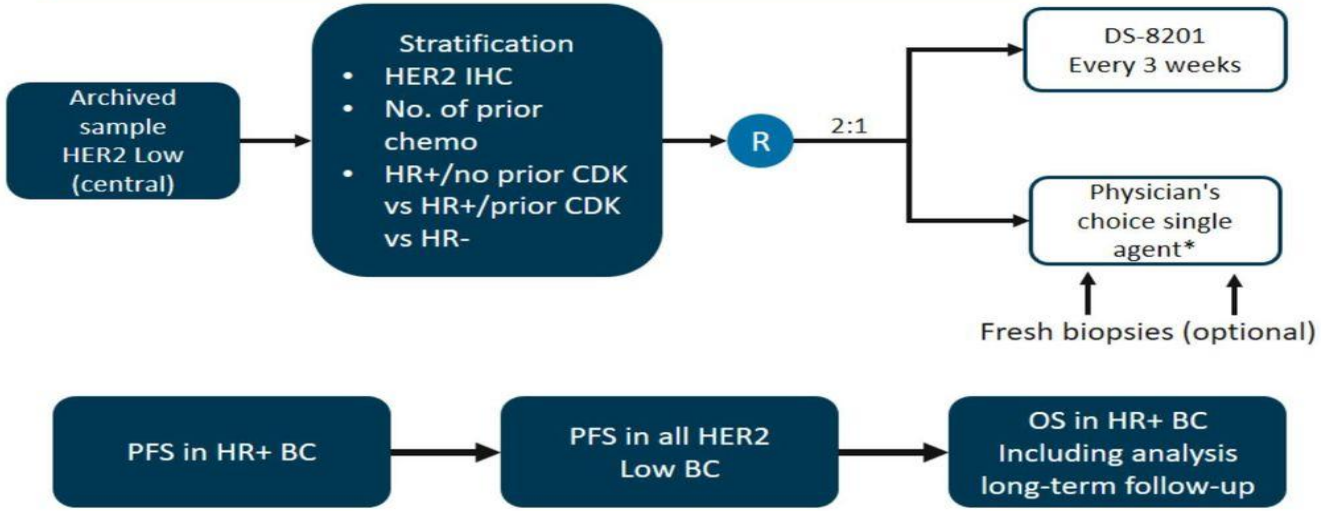
Her2 low subgroup:

- TNBC: 34% and ER+: 63%
- HER2 is not the oncogenic driver
- Benefit from ADC due to payload release before internalization – bystander effect
- Her2 low status variable over time



DESTINY-Breast04

HER2 Low Breast Cancer Phase 3 Study Design



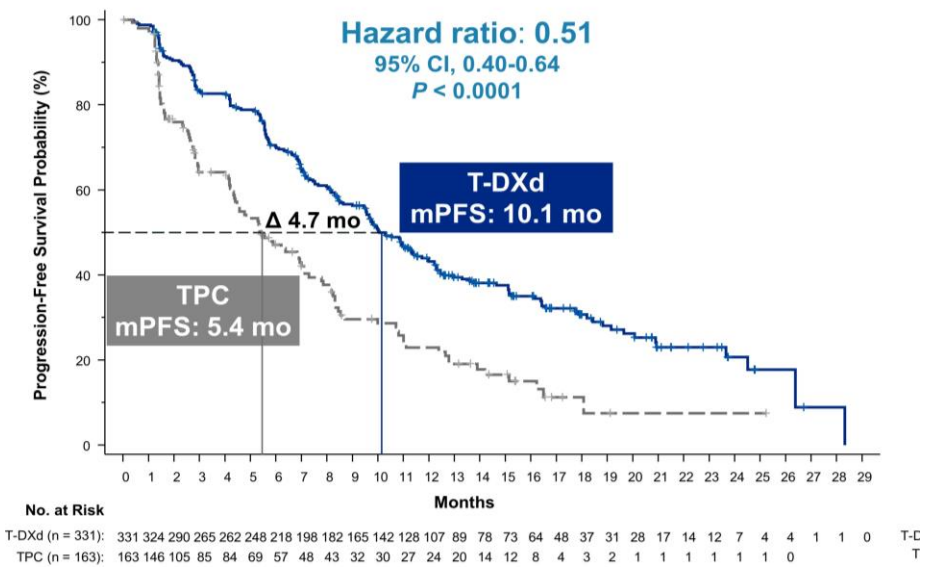
*Capecitabine/eribulin/gemcitabine/paclitaxel/nab-paclitaxel.
Modi S, et al. SABCS 2019. Abstract OT1-07-02.

Modi, S et al. *N Engl J Med*. 2022;387(1):9-20. Schmid P, et al. *J Clin Oncol*. 2021;39(15_suppl):1023.

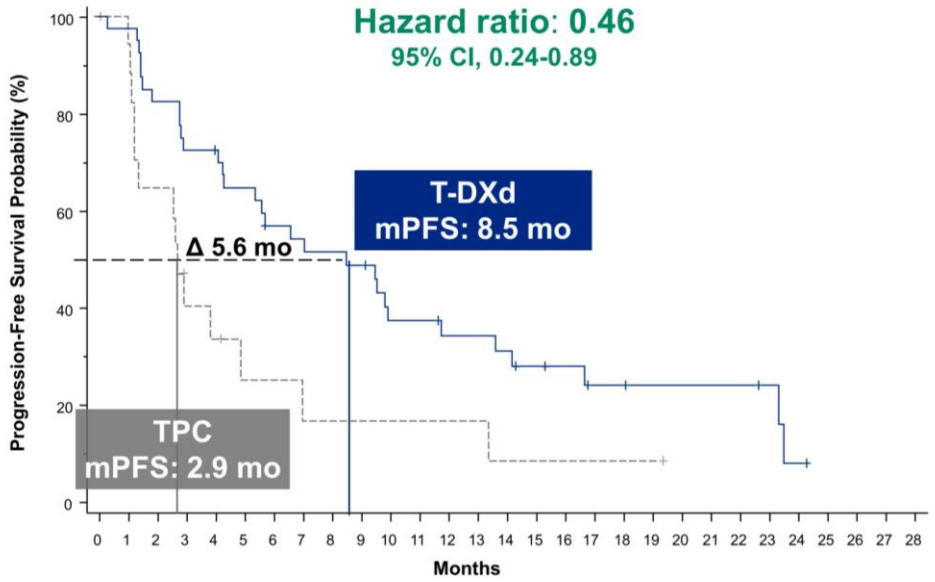
City of Hope

PFS

Hormone receptor–positive

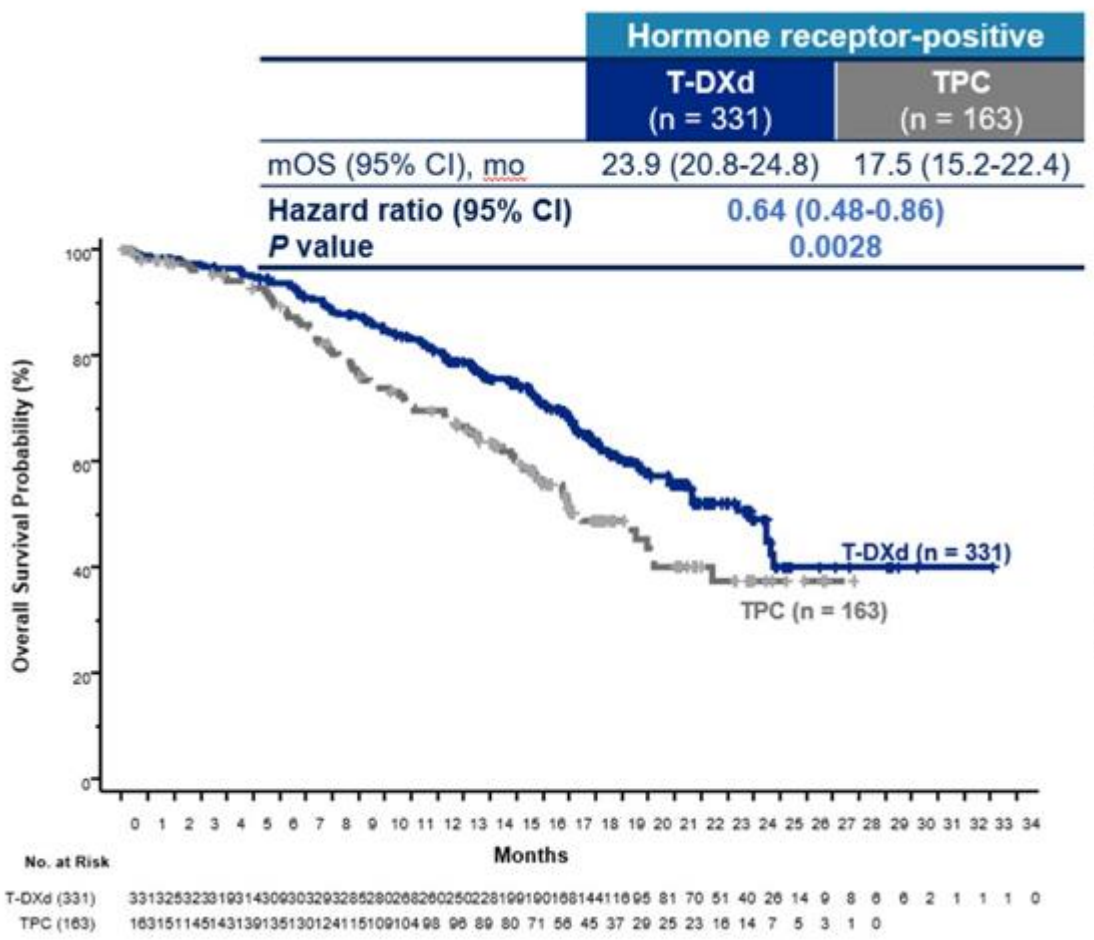


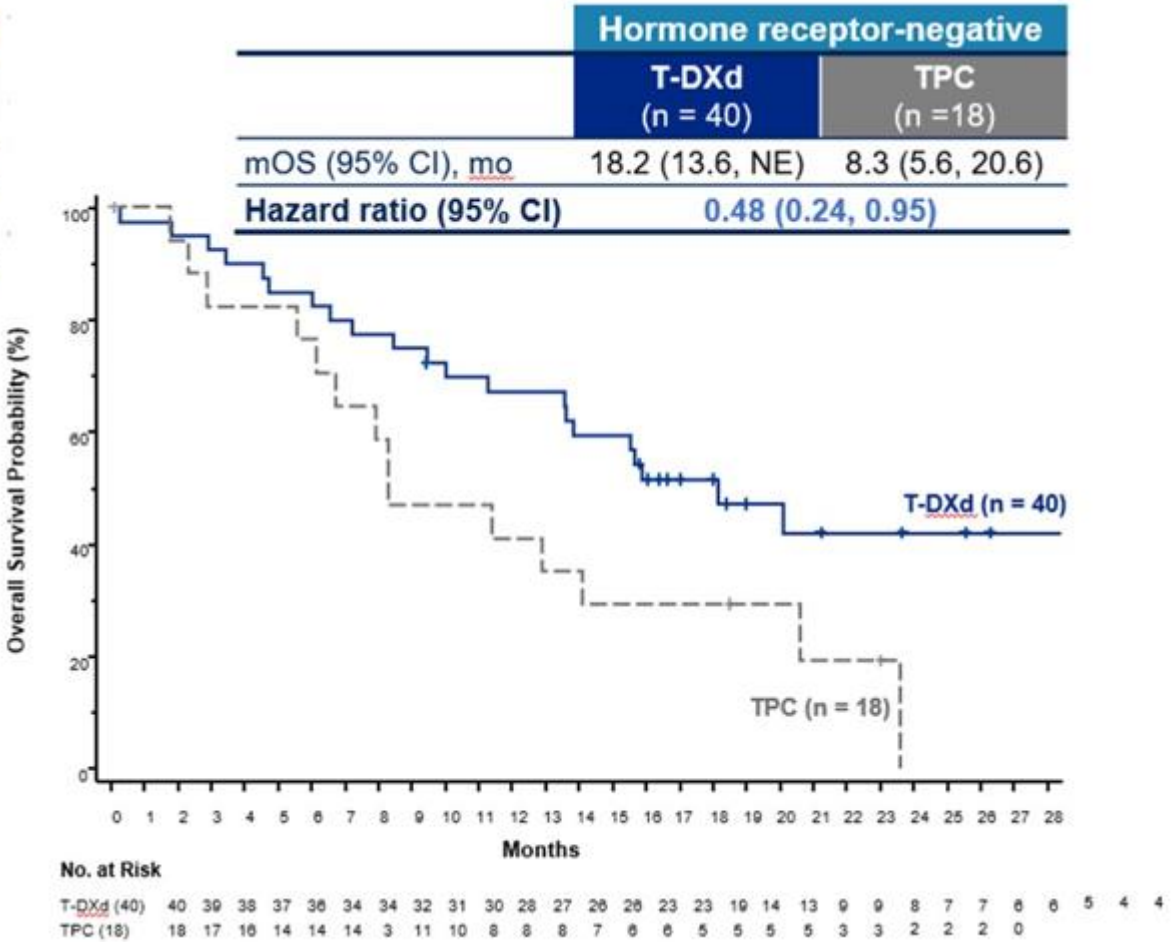
Hormone receptor-negative



Modi S, et al. Presented at ASCO 2022; *NEJM* 2022;387(1):9-20

OS in HR+ and HR - Patients

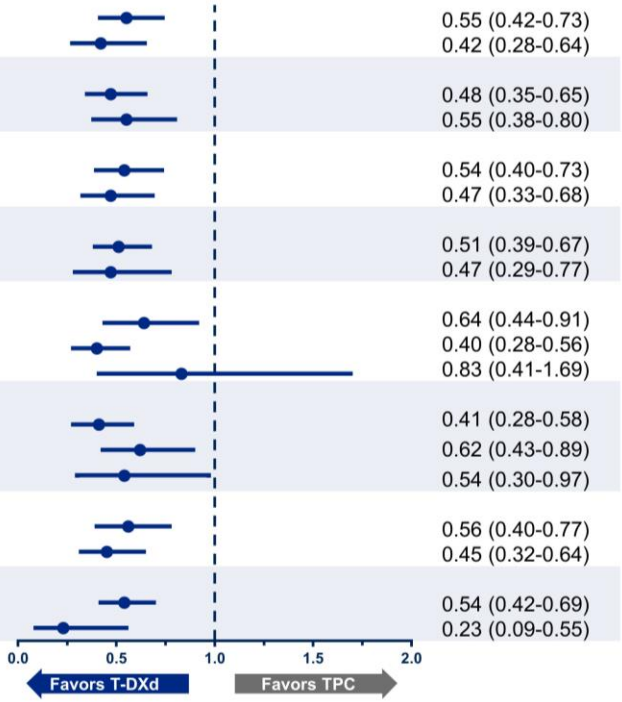




Modi S, et al. Presented at ASCO 2022; *NEJM* 2022;387(1):9-20

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.

T-DXd: 8.2% ILD

Modi S, et al. Presented at ASCO 2022; *NEJM* 2022;387(1):9-20

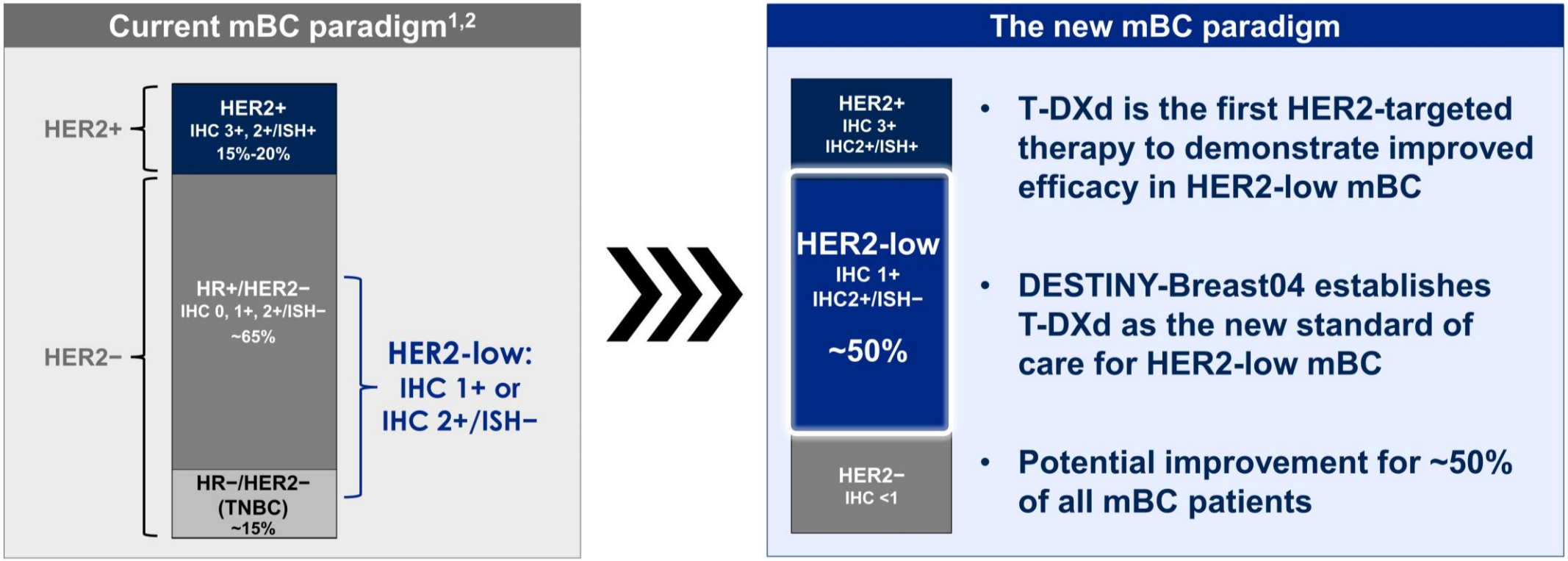
Overall Safety Summary

n (%)	Safety analysis set[a] T-DXd (n = 371)	TPC (n = 172)
Total patient-years of exposure, years[b]	283.55	63.59
TEAEs	369 (99)	169 (98)
Grade ≥3	195 (53)	116 (67)
Serious TEAEs	103 (28)	43 (25)
TEAEs associated with dose discontinuations	60 (16)	14 (8)
TEAEs associated with dose interruptions	143 (39)	72 (42)
TEAEs associated with dose reductions	84 (23)	66 (38)
TEAEs associated with deaths	14 (4)	5 (3)

- **Median treatment duration**
  - **T-DXd: 8.2 months (range, 0.2-33.3)**
  - **TPC: 3.5 months (range, 0.3-17.6)**
- Most common TEAE associated with treatment discontinuation
  - T-DXd: 8.2%, ILD/pneumonitis[c]
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction
  - T-DXd: 4.6%, nausea and fatigue[d]
  - TPC: 14.0%, neutropenia[d]
- Total on-treatment deaths[e]
  - T-DXd: 3.8%
  - TPC: 4.7%

DESTINY-Breast04 Summary and Impact

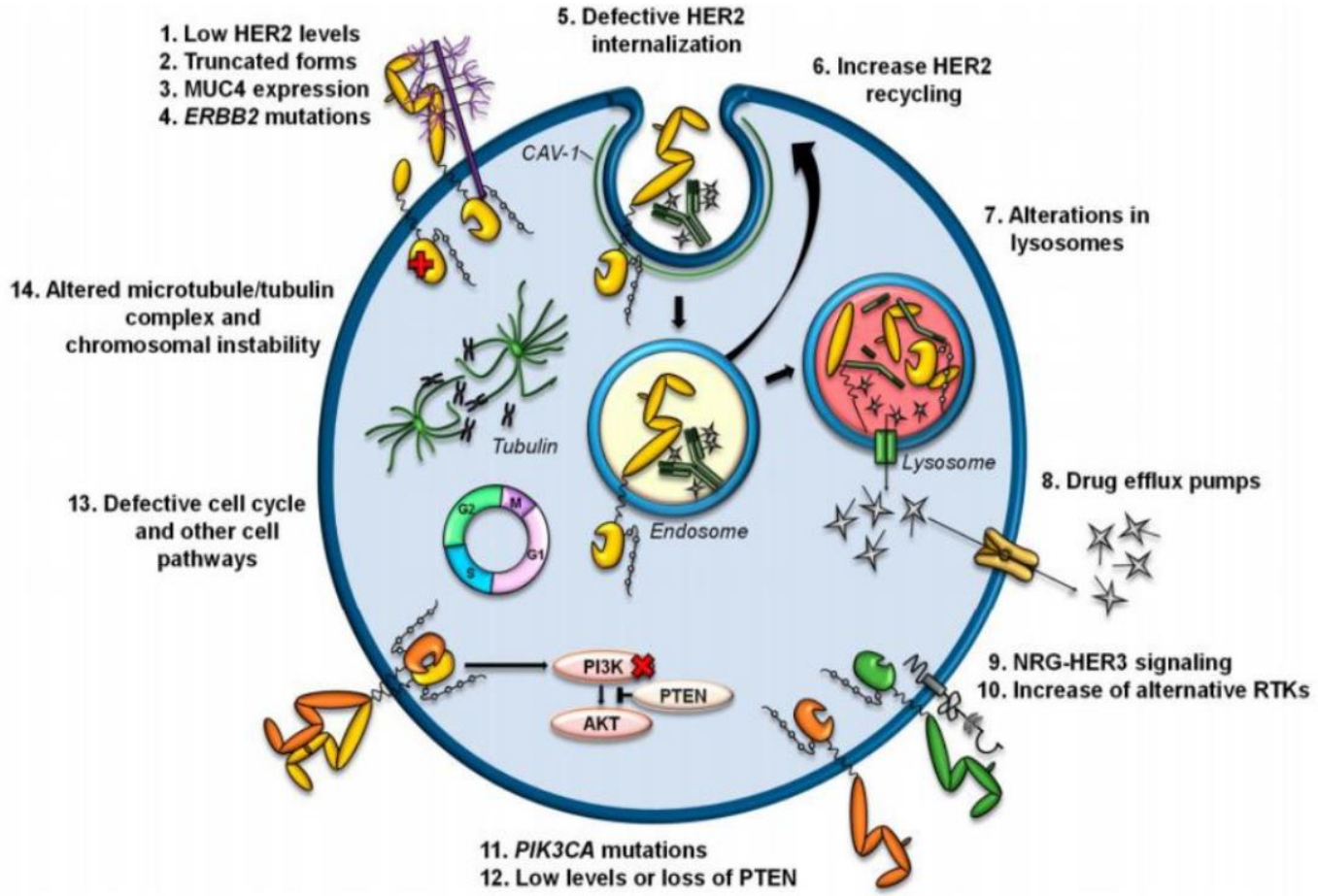
T-DXd treatment showed unprecedented improvement in efficacy for patients with HER2-low mBC



HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

1. Schettini F, et al. *NPJ Breast Cancer*. 2021;7(1):1. 2. Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-1962.

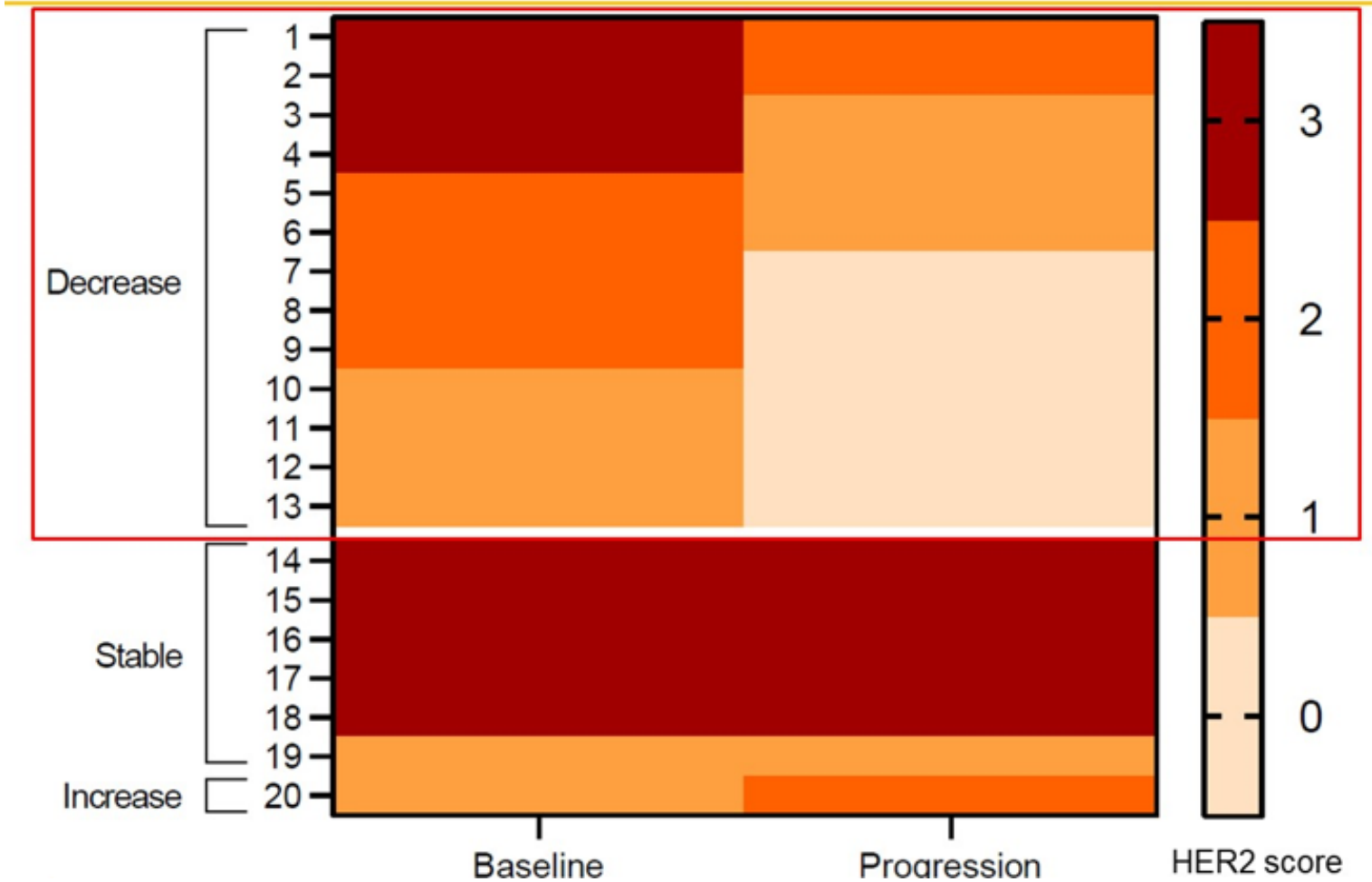
Mechanisms of resistance to ADCs



Diaz-Rodriguez E, et al. Cancers 2021

DAISY: Secondary Resistance

- 25 FFPE samples at baseline and progression: **9** HER2 IHC 3+ or IHC 2+/ISH+; **11** HER2 IHC 2+/ISH- or IHC 1+; **5** IHC 0
- HER2 status by standard IHC



13/20 (65%)
95% CI [40.8-84.6]

13 out of 20 (65%) patients presented a decrease of HER2 expression at progression

5 patients HER2 IHC 0: 4 stable and 1 to IHC

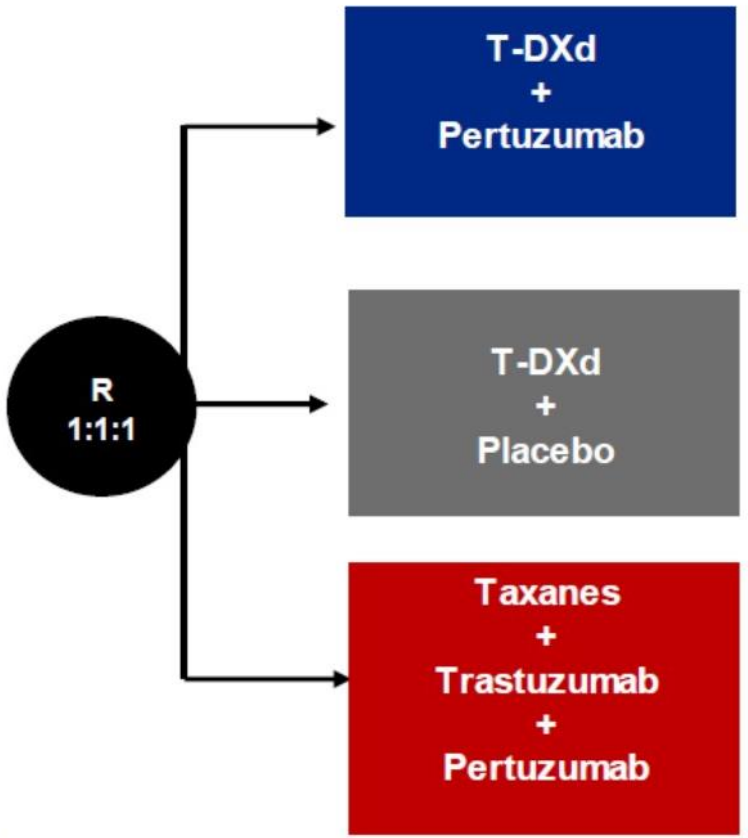
ESMO Breast 2022, Mosele, et al

T-DXd in the first-line setting

Destiny-Breast 09

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- No prior chemotherapy or HER2-targeted therapy for advanced or metastatic breast cancer. Participants who have received chemotherapy or HER2-targeted therapy in the neoadjuvant or adjuvant setting are eligible if > 6 months from treatment to metastatic diagnosis
- Could have clinically stable, treated brain metastases

Stratification factors
- Hormone receptor status
- De novo versus recurrent disease
- Detection of *PIK3CA* mutation



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

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

NCT04784715

BRIDGET/BRE21-516: Single arm, phase II, multicenter, clinical trial of tucatinib added to trastuzumab/pertuzumab or T-DM1 in patients with isolated intracranial progression in HER2+ advanced breast cancer

- Advanced HER2+ BC
- Adjuvant or Metastatic HP/T-DM1
- Stable extracranial disease
- 1st or 2nd intracranial event

ER+/HER2+ disease allowed, endocrine therapy can continue

N=50

Local therapy with stereotactic radiosurgery +/- surgical resection if indicated

Tras/pertuz + tucatinib

T-DM1 + tucatinib

Staging q9 weeks: MRI brain, systemic

Extracranial Progression

Tucatinib

Tras/pertuz → T-DM1 → Tras/Capecitabibe

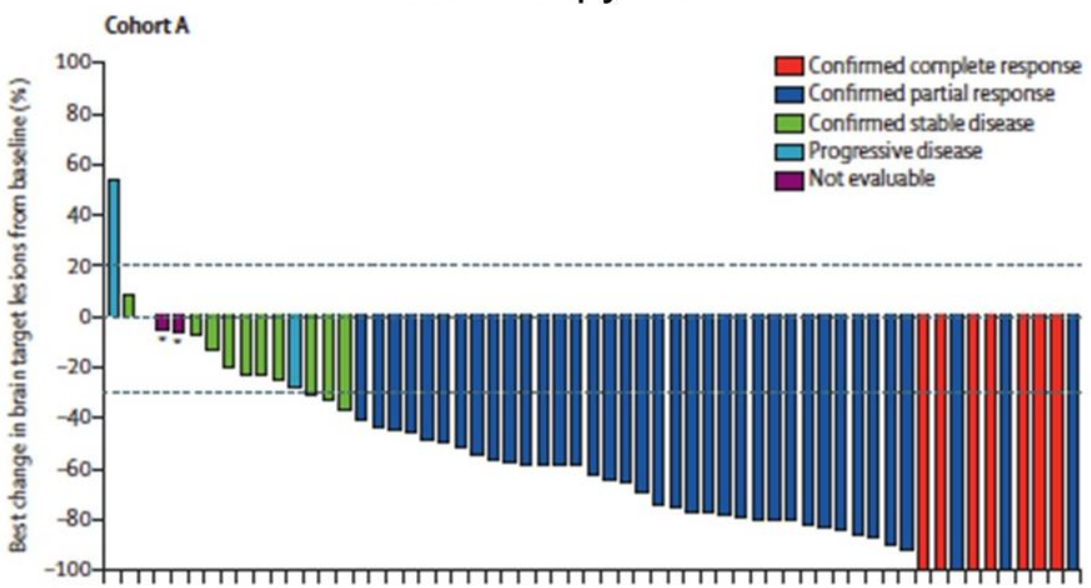
★ If intracranial disease stable with extracranial progression, continue tucatinib into next line

Primary objective: Intracranial PFS (RANO-BM)
Secondary objectives: PFS, 2nd intracranial PFS, OS, CBR, PROs, safety, time to next line therapy

Sarah Sammons/Carey Anders

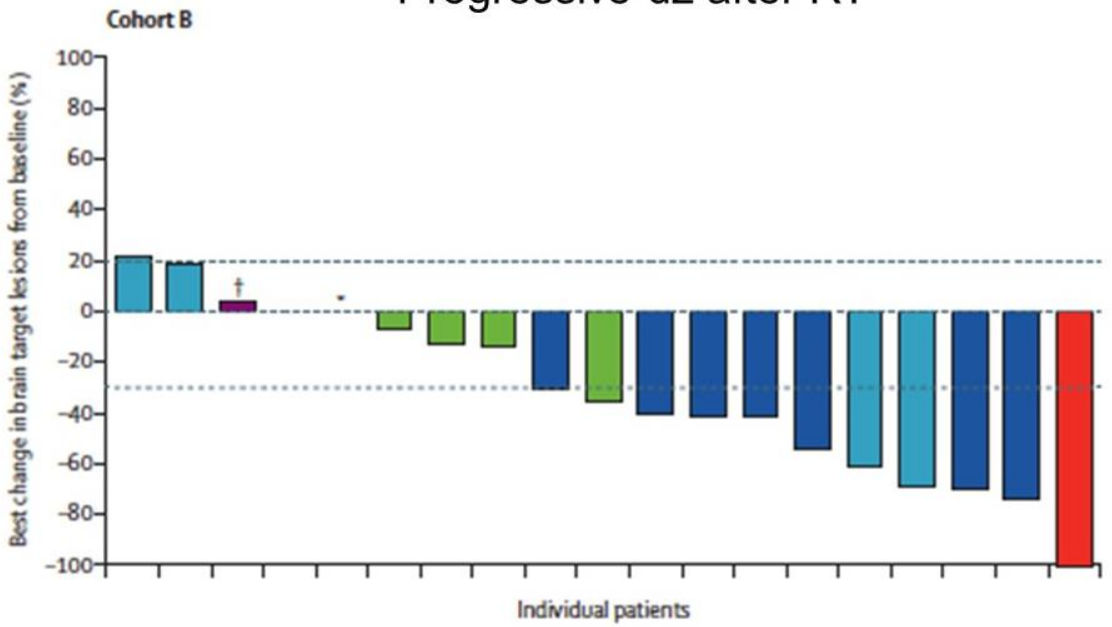
PERMEATE: Pyrotinib + capecitabine for HER2+ BCBM

Radiotherapy-naïve



Intracranial ORR 74.6%

Progressive dz after RT



Intracranial ORR 42.1%

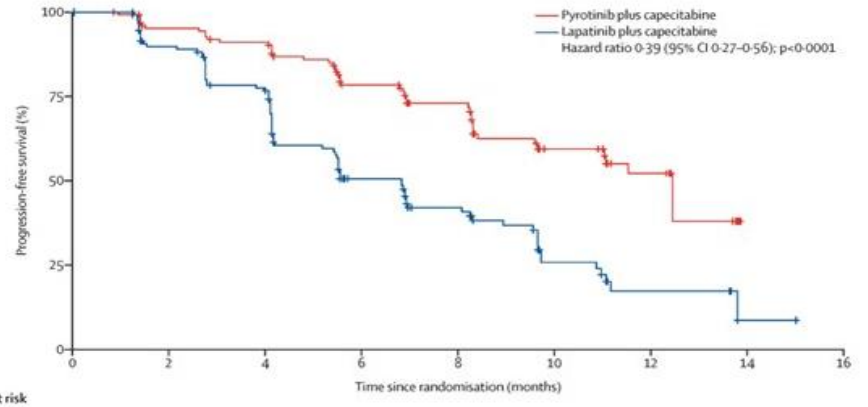
Across both cohorts, most pts had prior trastuzumab; 2-5% of pts prior pertuzumab; only 3 pts (in Cohort B) had prior TDM1
Cohort A: 85% of pts 0-1 prior MBC lines; Cohort B: 53% of pts 0-1 prior MBC lines

Yan et al, Lancet Oncol 2022

Pyrotinib

PFS

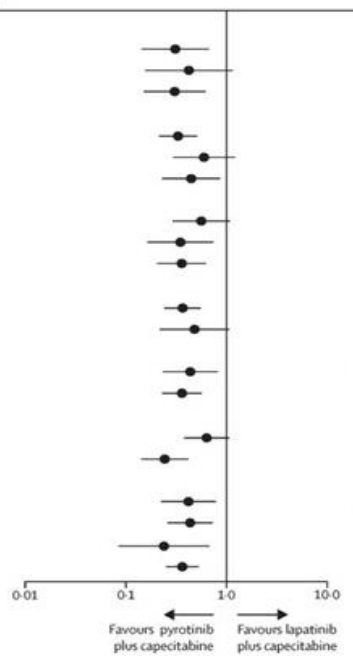
A



Number at risk (number censored)									
Pyrotinib plus capecitabine	134 (0)	116 (12)	110 (13)	76 (33)	58 (46)	32 (62)	18 (73)	0 (88)	–
Lapatinib plus capecitabine	132 (0)	112 (7)	92 (11)	49 (24)	34 (31)	14 (40)	6 (44)	1 (47)	0 (48)

B

	Pyrotinib plus capecitabine group (n/N)	Lapatinib plus capecitabine group (n/N)	Hazard ratio (95% CI)
Trastuzumab therapy for metastatic disease			
<3 months	14/28	18/21	0·31 (0·14–0·67)
3–6 months	5/12	19/31	0·42 (0·16–1·15)
≥6 months	12/39	26/37	0·31 (0·15–0·62)
Trastuzumab resistance*			
No	31/97	67/100	0·33 (0·21–0·51)
Yes	15/37	17/32	0·60 (0·29–1·21)
HER2 amplification by FISH	14/36	30/50	0·45 (0·23–0·86)
Pathological grading			
II	15/42	23/36	0·56 (0·29–1·09)
III	11/45	20/37	0·35 (0·16–0·74)
Unknown	20/47	37/55	0·36 (0·20–0·63)
Metastatic sites			
Visceral	35/103	69/108	0·37 (0·24–0·56)
Non-visceral	11/31	15/24	0·48 (0·22–1·06)
ECOG status			
0	17/47	24/43	0·44 (0·23–0·82)
1	29/87	60/89	0·36 (0·23–0·57)
Oestrogen and progesterone receptor status			
Positive†	26/62	36/58	0·63 (0·38–1·06)
Negative	20/72	48/74	0·24 (0·14–0·42)
Previous lines of chemotherapy for metastatic disease			
0	18/57	24/46	0·42 (0·22–0·78)
1	22/56	46/65	0·44 (0·26–0·73)
2	6/21	14/21	0·24 (0·08–0·67)
All patients	**46/134**	**84/132**	**0·36 (0·25–0·53)**

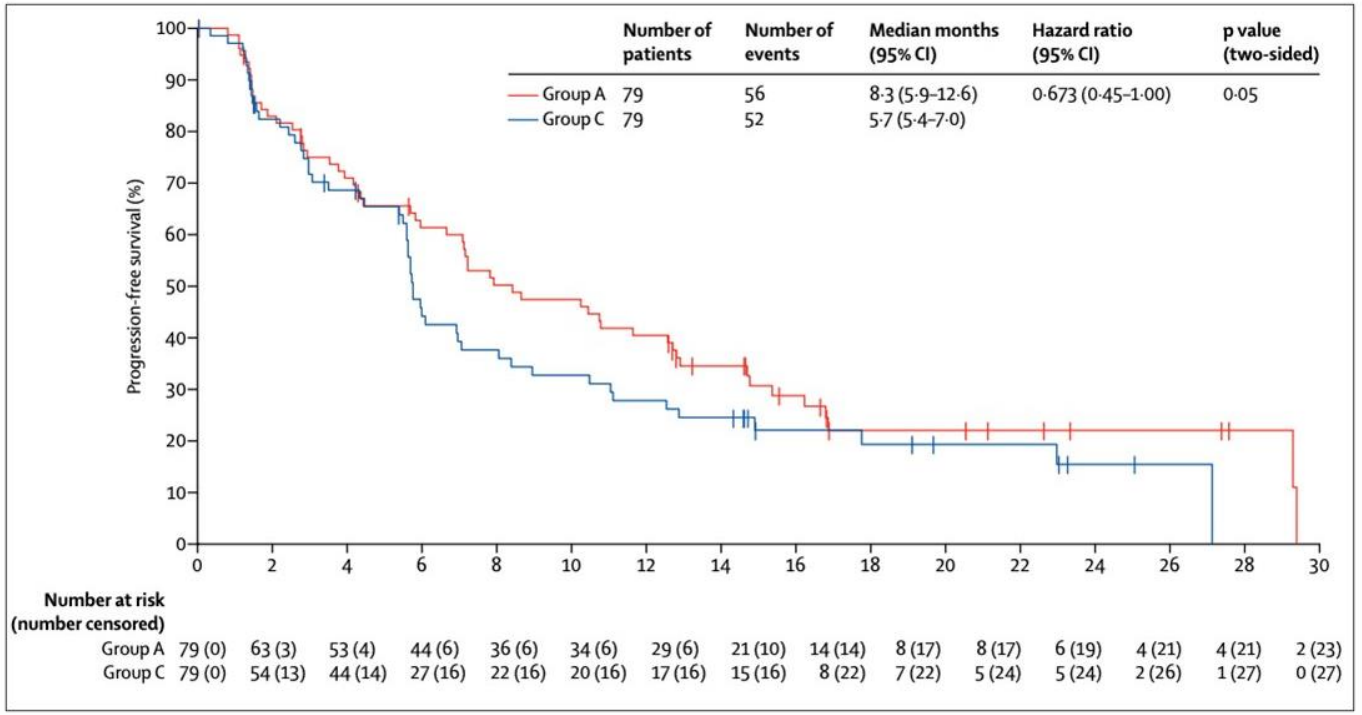


Xu B et al. Lancet Oncol. 2021 Mar;22(3):351-360..

monarcHER: abemaciclib + trastuzumab + fulvestrant

About 50% of HER2+ MBC coexpress HR (triple positive). Could CDK4/6 inhibition improve outcomes after progression to several lines of treatment?

In a randomized phase 2 trial (n=237), abemaciclib + trastuzumab + fulvestrant outperformed chemo + trastuzumab in patients with triple positive MBC (mPFS 8.3 vs 5.7 months)



Tolaney SM et al. *Lancet Onc* 2020

Other anti-HER2 treatments: trastuzumab duocarmazine

Novel anti-HER2 ADC, based on trastuzumab and a cleavable linker-duocarmycin payload (alkylator)

TULIP trial

HER2-positive LABC or MBC
≥2 therapies for metastatic disease, or T-DM1 for metastatic disease
Treated brain mets are allowed
N=437

R 2:1

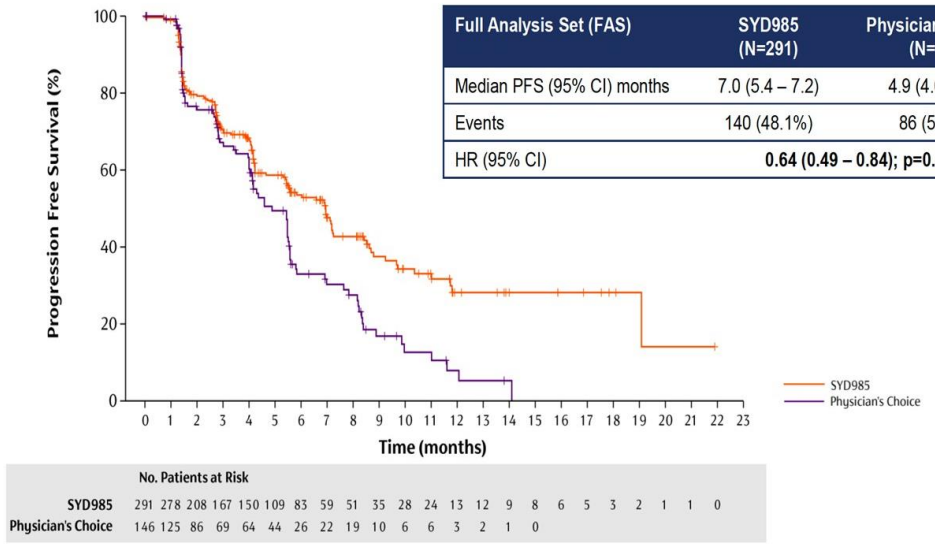
SYD985 treatment
1.2 mg/kg IV every 21 days
N=291

Physician's choice treatment (PC)
N=146

Continue treatment until progression or unacceptable toxicity

Primary Endpoint
- Centrally assessed PFS

Secondary Endpoints
- Investigator assessed PFS
- OS
- ORR
- HRQOL



Full Analysis Set (FAS)	SYD985 (N=291)	Physician's choice (N=146)
Median PFS (95% CI) months	7.0 (5.4 – 7.2)	4.9 (4.0 – 5.5)
Events	140 (48.1%)	86 (58.9%)
HR (95% CI)	**0.64 (0.49 – 0.84); p=0.002**	

Significant improvement in PFS. Similar ORR (28% vs 29%), no significant difference in OS

Main TRAEs: ocular AEs, GI toxicity, interstitial lung disease (7.6%)

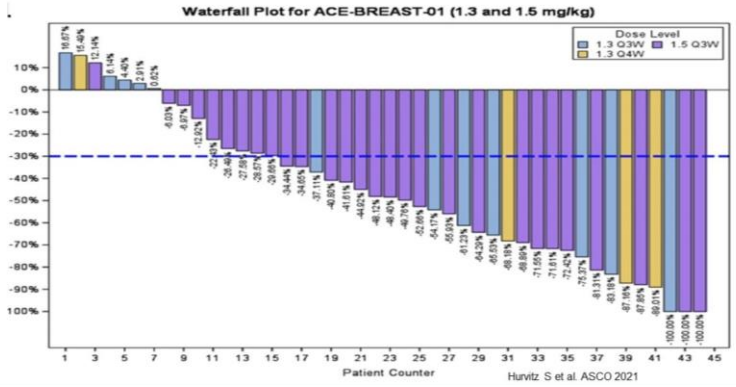
Saura C et al. ESMO 2021

ARX788

Novel anti-HER2 ADC, consisting of trastuzumab site-specifically conjugated to the tubulin inhibitor AS269

Phase 1 trial: ORR 50-66% among 108 heavily pretreated HER2+ MBC patients

Main TRAEs: ocular AEs, interstitial lung disease (34%), transaminitis

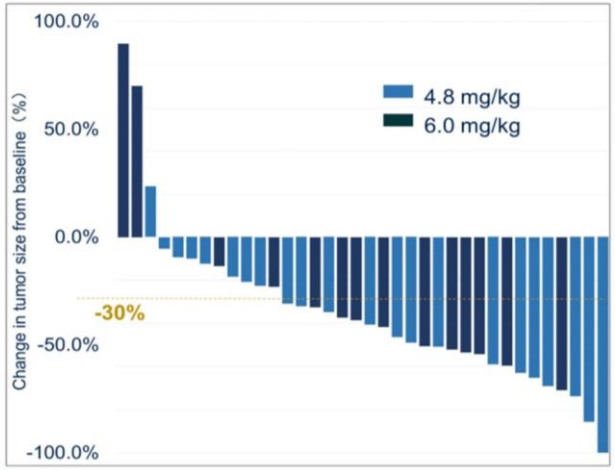


A166

Novel anti-HER2 ADC, consisting of trastuzumab site-specifically conjugated to the anti microtubule agent Duo-5

Phase 1 trial: ORR 60-70% among 36 heavily pretreated HER2+ MBC patients

Main TRAEs: ocular AEs, peripheral neuropathy, electrolyte imbalances

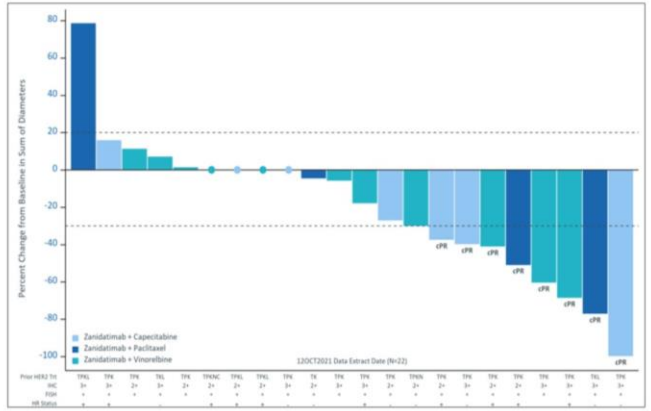


Zanidatamab (ZW25) + chemotherapy

HER2-targeted bispecific antibody targeting both trastuzumab and pertuzumab binding domains

Phase 1 trial: ORR 36% and median PFS 7.3 months among 24 pretreated HER2+ MBC patients

Main TRAEs: diarrhea, infusion-related reactions



Hu X et al. ASCO 2021; Presented at ASCO 2022 by Giuseppe Curigliano

Hurvitz S et al. SABCS 2021

Barriers to clinical trial enrollment in racial and ethnic minority patients

- Enrollment in African American patients lower than whites
- Enrollment in clinical trials between 2 cohorts of patients, 2001-2010 with 1990-2000 compared and showed more diversity
- In 1990-2000: **89% white**, **10.5% African American, 0.4% Hispanic** and **0.04% Asian**
- 2001-2010: **82.9% white**, **6.2% African American, Asian 3.3%, 2.2% Hispanic**, **Native American 0.1%**
- Barriers: System: limited number of available studies since a lot of minorities receive care at under resourced centers, lack of community practice engagement
    - Individual (healthcare professional, patient and family)
    - Interpersonal level: doctor-patient relationship
- Open discussion about past abuse of minorities in research to create and sustain partnership in community
- Minority based community clinical oncology program of NCI and to include patient advocacy group to work on future plans to increase minority enrollment
- To improve the funding for all clinical trials within NCI
- Awareness – sensitivity - knowledge - skills

Hamel et al. Cancer Control 2016; 23(4) 327-337

NCCN Guidelines-Version 3.2022

HER2-Positive			
Setting	**Regimen**	**NCCN Category of Preference**	**NCCN Category of Evidence**
First line[j]	Pertuzumab + trastuzumab + docetaxel[k]	Preferred Regimen	1
	Pertuzumab + trastuzumab + paclitaxel[k]	Preferred Regimen	2A
Second line[j]	Fam-trastuzumab deruxtecan-nxki[j,l,m]	Preferred Regimen	1
	Ado-trastuzumab emtansine (T-DM1)[j]	Other Recommended Regimen	2A
Third line and beyond (optimal sequence is not known)	Tucatinib + trastuzumab + capecitabine[k,n]	Other Recommended Regimen[n]	1
	Trastuzumab + docetaxel or vinorelbine[k,o]	Other Recommended Regimen	2A
	Trastuzumab + paclitaxel ± carboplatin[k,o]	Other Recommended Regimen	2A
	Capecitabine + trastuzumab or lapatinib[k,o]	Other Recommended Regimen	2A
	Trastuzumab + lapatinib[k,o] (without cytotoxic therapy)	Other Recommended Regimen	2A
	Trastuzumab + other agents[k,o,p,q]	Other Recommended Regimen	2A
	Neratinib + capecitabine[o]	Other Recommended Regimen	2A
	Margetuximab-cmkb + chemotherapy[o] (capecitabine, eribulin, gemcitabine, or vinorelbine)	Other Recommended Regimen	2A
Additional targeted therapy options (See BINV-R)			

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

ASCO Guidelines Update 2022

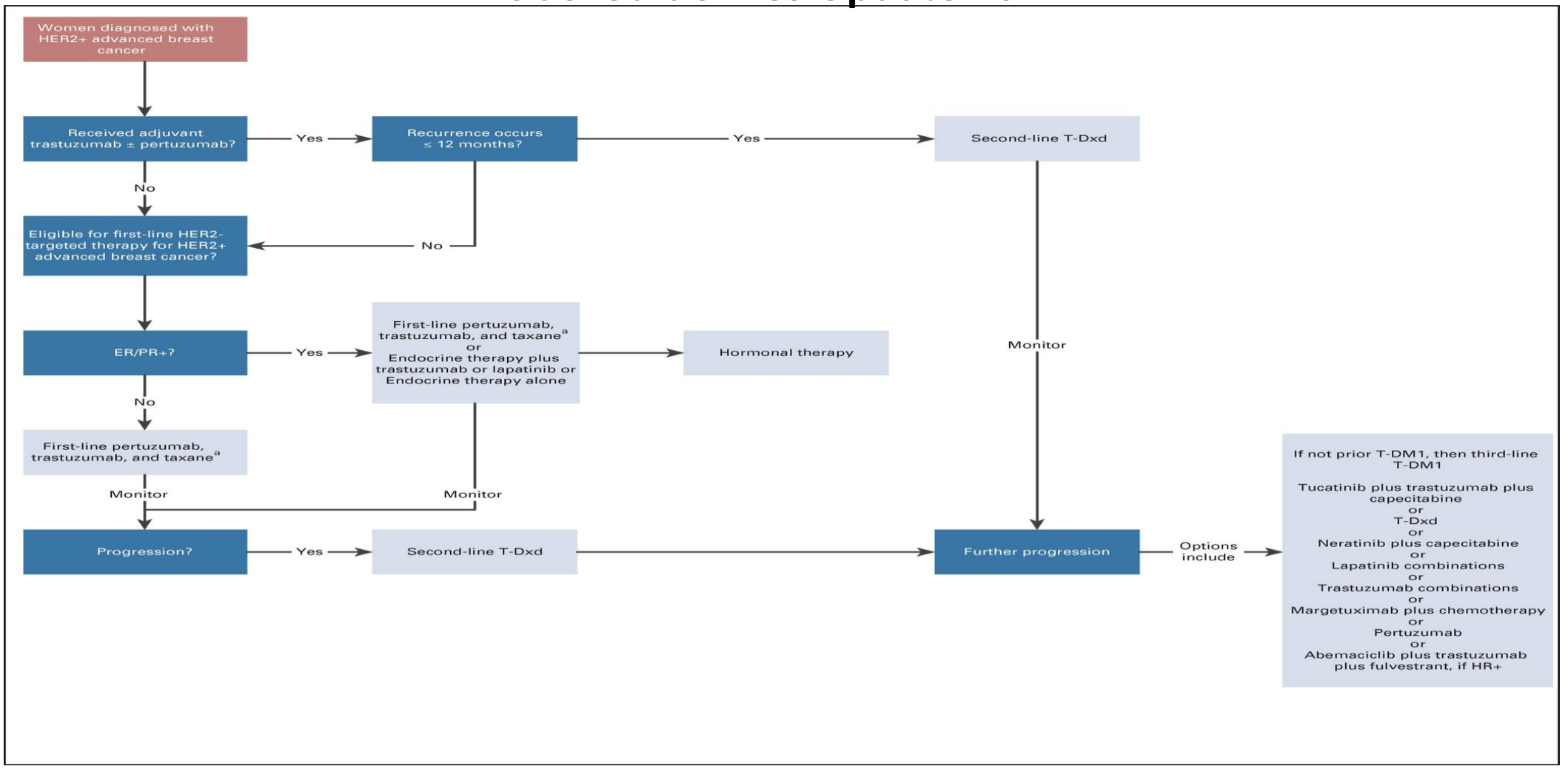
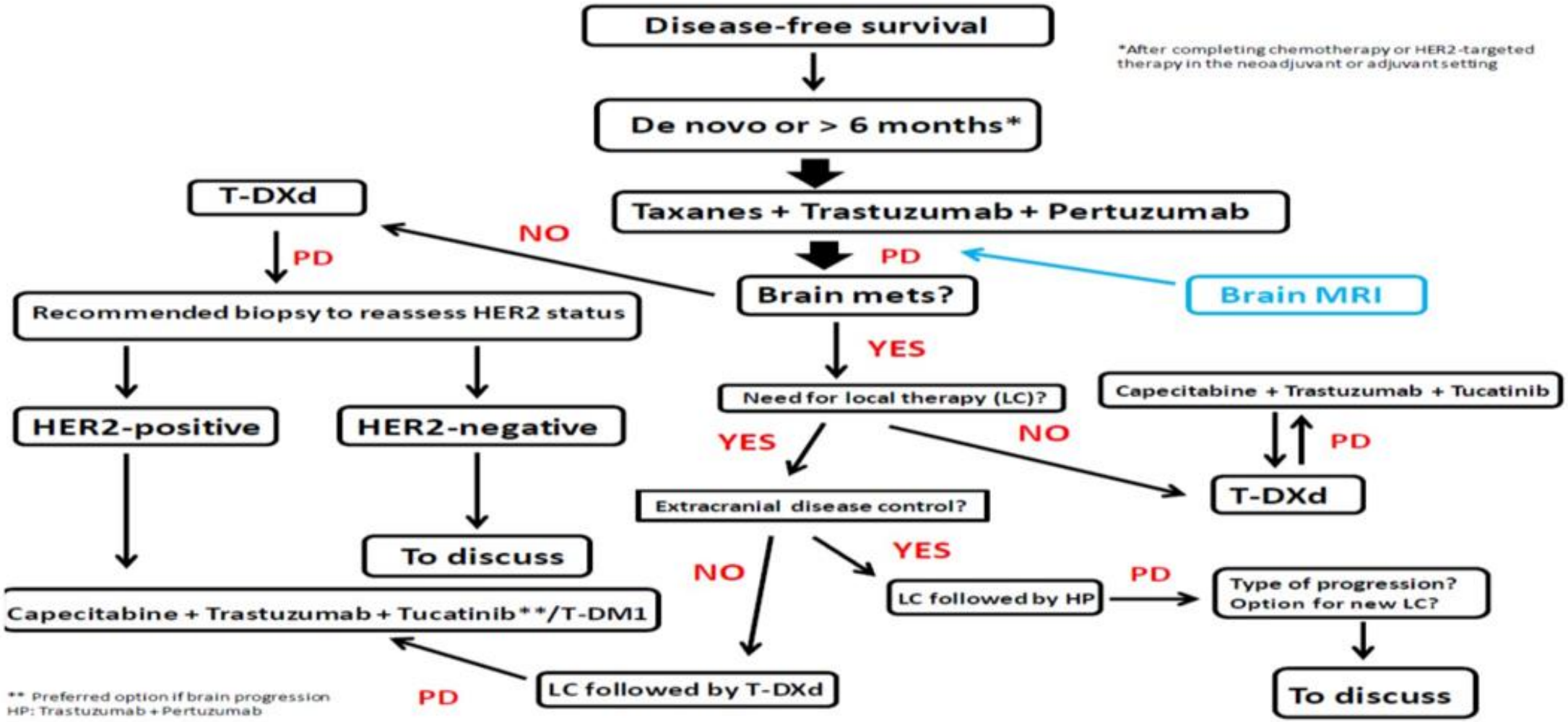


FIG 1. Treatment algorithm. If the patient is receiving HER2-targeted therapy and chemotherapy combinations, provide chemotherapy for 4-6 months and/or to the time of maximal response, if low toxicity and no progression. Continue HER2-targeted therapy after stoppage of chemotherapy. aExcept if contraindications to taxanes. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; T-DM1, trastuzumab emtansine; T-Dxd, trastuzumab deruxtecan.

Published in: Sharon H. Giordano; Maria Alice B. Franzoi; Sarah Temin; Carey K. Anders; Sarat Chandarlapaty; Jennie R. Crews; Jeffrey J. Kirshner; Ian E. Krop; Nancy U. Lin; Aki Morikawa; Debra A. Patt; Jane Perlmutter; Naren Ramakrishna; Nancy E. Davidson; ***Journal of Clinical Oncology*** **2022 402612-2635.**

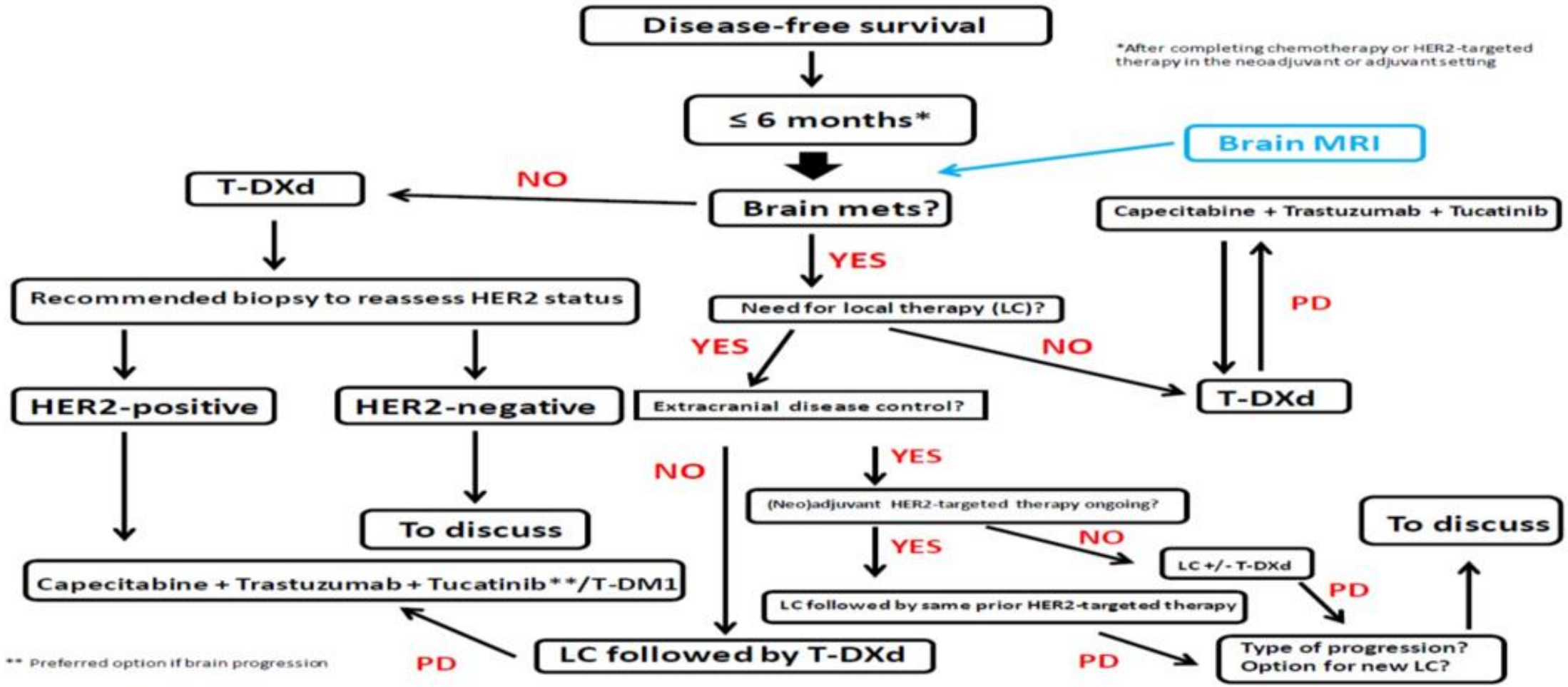
DOI: 10.1200/JCO.22.00519

Conclusions



Courtesy Jose Perez-Garcia

Conclusions II



Courtesy Jose Perez-Garcia

Future Directions

- Significant advances in the management of Her2 positive breast cancers are made
- Strategies to control the cost of cancer care, choosing wisely and bridging the gap and disparities in oncology care

" Science will only fulfill its promises when the benefits are equally shared by the really poor of the world"

Cesar Milstein (Noble Prize recipient in 1984)