HER2 disease: Amplification, Overexpression and Mutation in Breast Cancer

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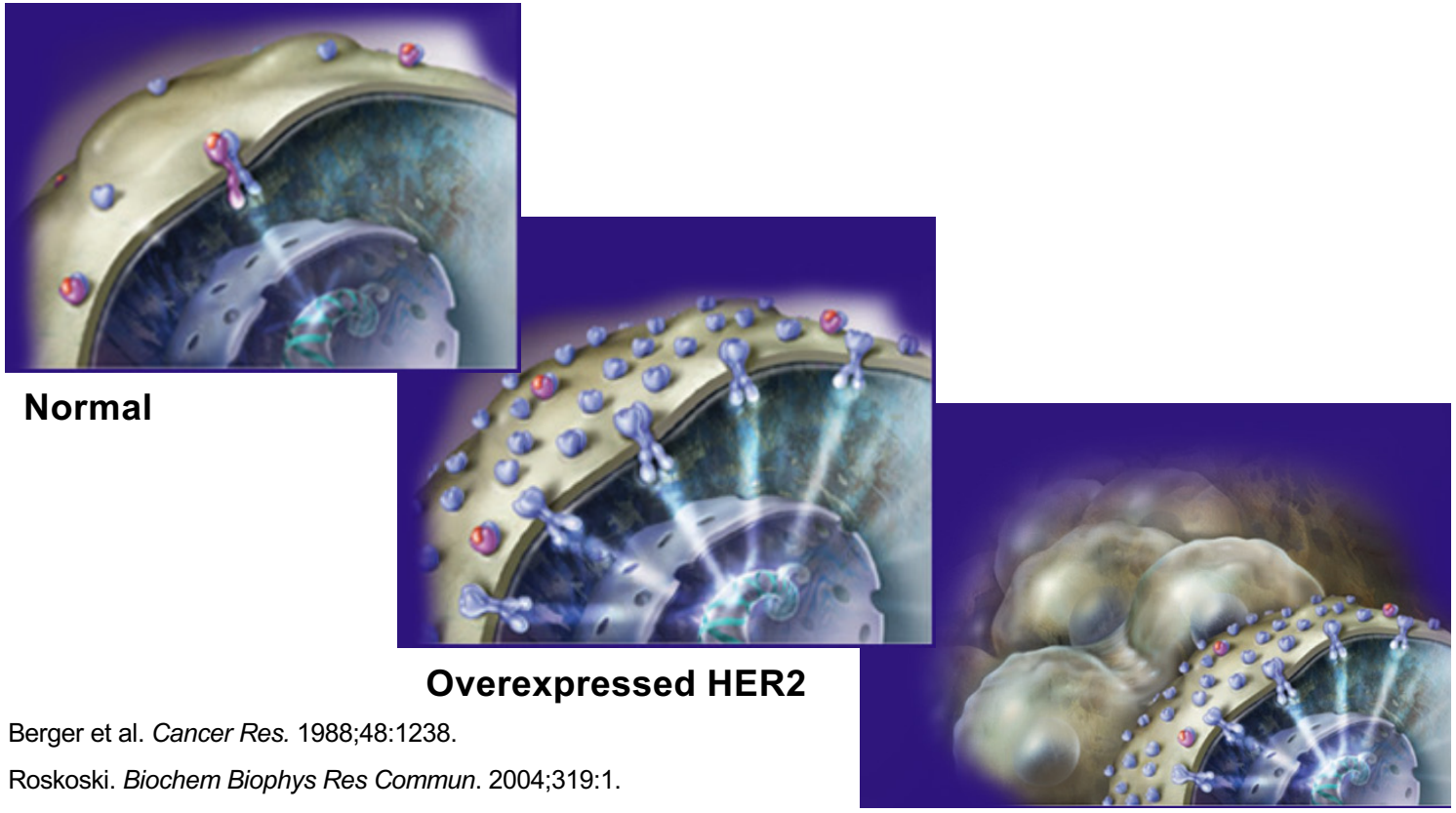
Objectives

1. Summarize the key advances in HER 2 -breast cancer that led to today's understanding of how the gene affects breast cancer.

2. Apply these latest advances in understanding HER2 in clinical practice to how we currently decide breast cancer treatment strategies.

3. Understand the variations that can occur across a patient's clinical course and how to adapt therapy accordingly for the management of patients with HER 2 breast cancer.

HER2 Overexpression and Amplification Signals Cells to Divide



Normal

Overexpressed HER2

Excessive cellular division

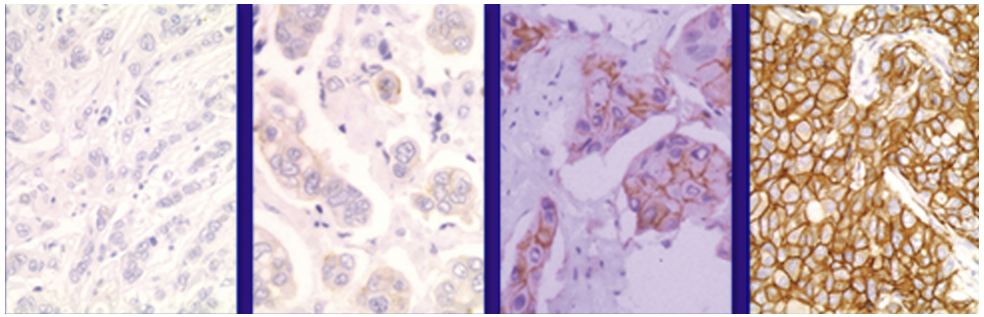
Berger et al. *Cancer Res.* 1988;48:1238.

Roskoski. *Biochem Biophys Res Commun*. 2004;319:1.

Rowinsky. *Annu Rev Med*. 2004;55:433.

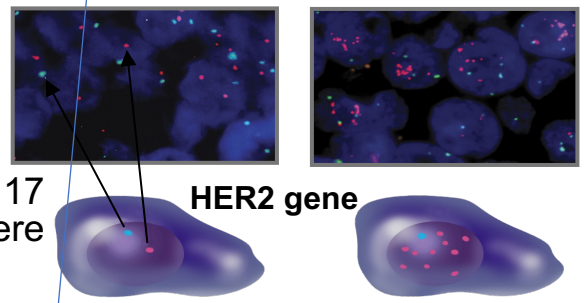
Slamon et al. *Science*. 1987;235:177.

HER2 Protein Overexpression and Amplification for Clinical Discrimination



IHC 0 IHC I+ IHC 2+ IHC 3+

Her 2 negative



HER2-normal Ratio <2.0

HER2-amplified Ratio ≥2.0

Her 2 Positive

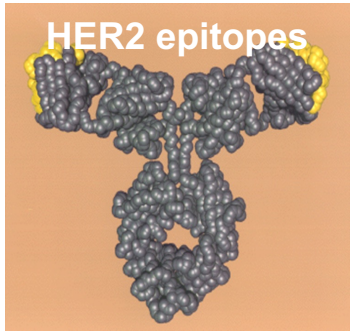
Treatment pathway follows the ER status

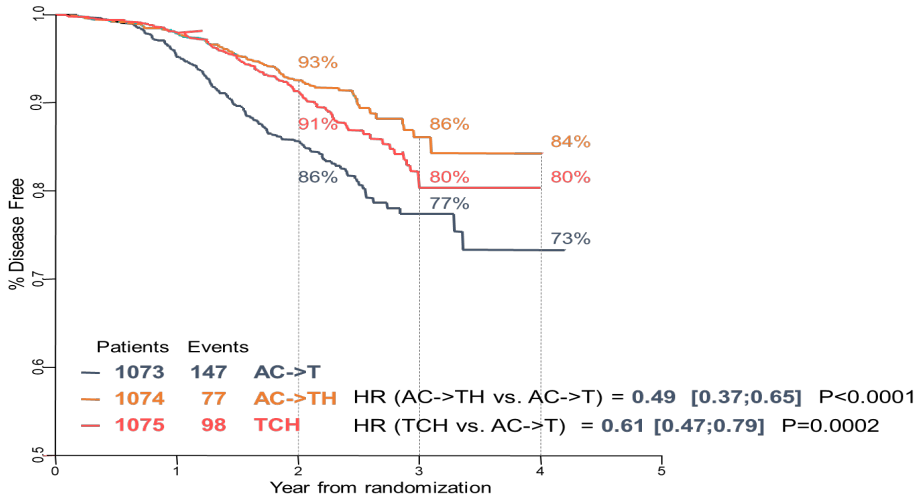
Her 2 Low treatment pathway in MBC

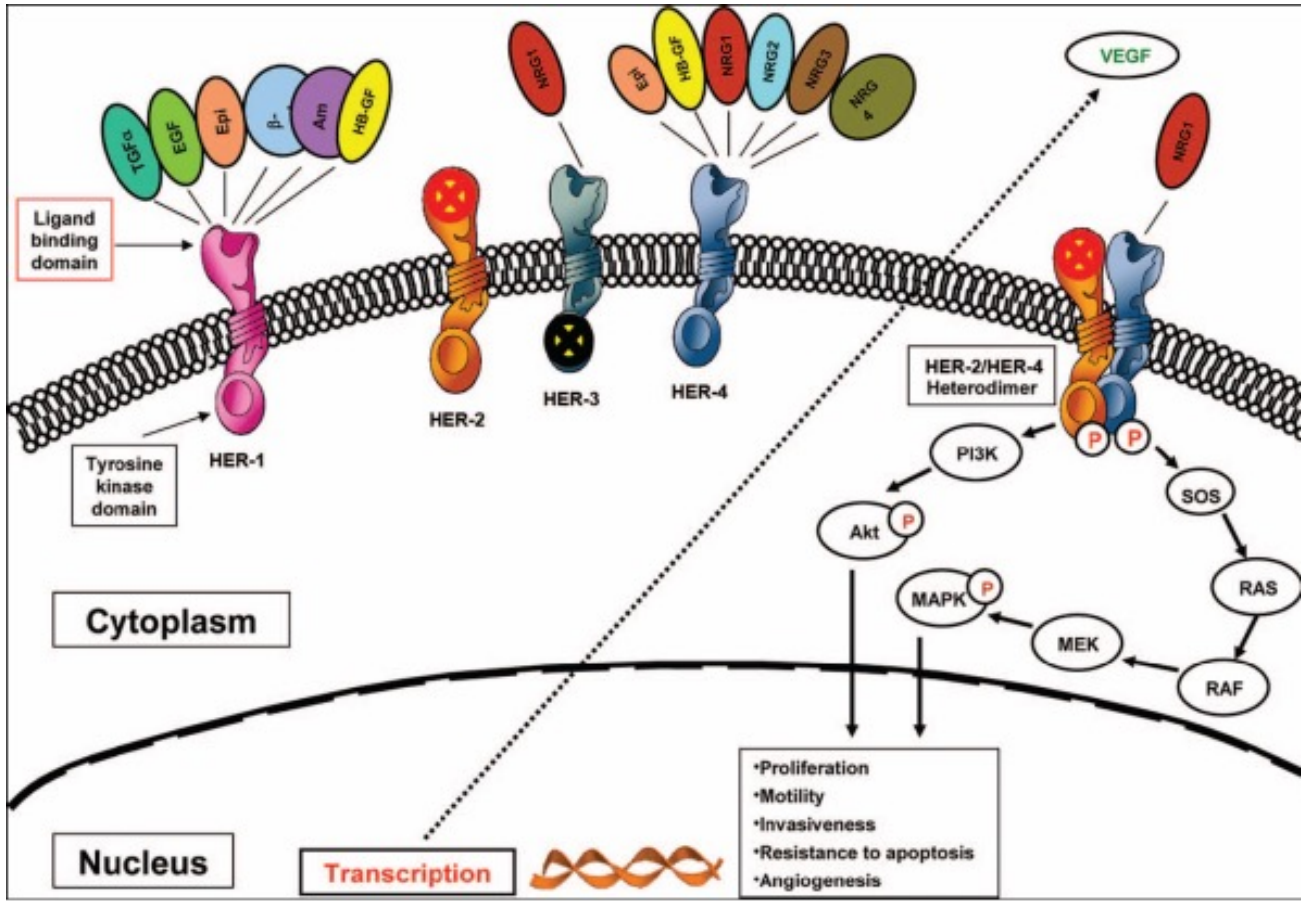
Treatment driven down the Her 2 pathway

HER2 can be therapeutically hit

1. **through its ligand binding domain**
2. **Through its TK domain**







Trastuzumab: Humanized Anti-HER2 MAb

The mABs trastuzumab and pertuzumab in the Neoadjuvant Space

Study	Regimen	Phase/Size	pCR	Disease outcomes
NOAH trial	SOC chemo +/- H	II/235	43% v 58%	HR 0.64
TRYPHAENA	FEC-THP FECHP-THP TCHP	II/150	55% 56% 64%	DFS 87-90%
TRAIN-2	FEC-TCHP TCHP		67% v 68%	EFS 93%, OS 98% both arms
KRISTINE	TDM-1P TCHP	III/444	44% 55.7%	
NeoSPhere	TH [FEC H adj.] THP HP TP	II/417	29% 45.8% 24% 17%	PFS 81% 86% 73% 73%

These significant studies paved the way for TCHP to become a standard neoadjuvant regimen moving forward.

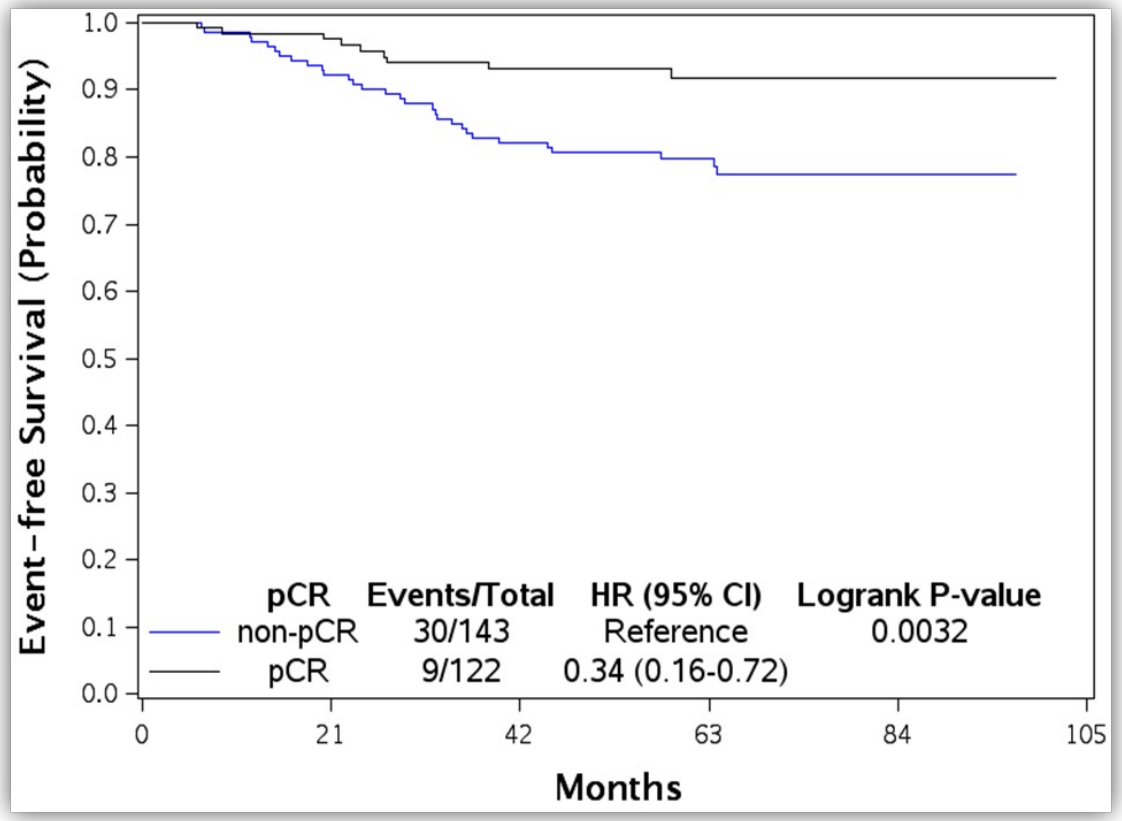
Gianni, Lancet Oncol 2014.
Schneeweiss, Eur J Cancer 2018
Hurvitz Lancet Oncol 2018
Gianni, Lancet Oncol 2014
Sikov W. 2021 https://doi.org/10.1007/978-3-030-88020-0_6

The neoadjuvant era highlighted the role of pCR in survival for Her 2 + early breast cancer

Patients with residual invasive breast cancer after completion of preoperative HER2-directed therapy and chemotherapy have an inferior prognosis [2-6]

Investigation of additional treatment strategies warranted

CALGB 40601



Krop et al, AACR-SABCS 2017

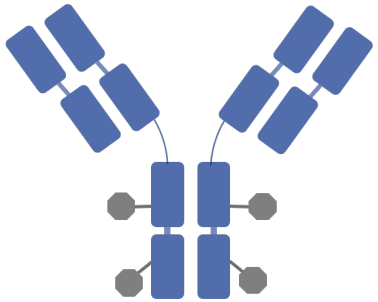
RD: ~80 % 5y EFS

Untch et. al. JCO 2011[2]; Cortazar et al. Lancet 2014[3]; de Azambuja et. al Lancet Oncol 2014[4]; Gianni et al.,Lancet Oncol 2014[5]; Schneeweiss et al., Eur J Cancer 2018[6]

HER2-Targeting Antibody-Drug Conjugates (ADCs)

ADC Attributes	T-DM1[3-5]
Payload MoA	Anti-microtubule
Drug-to-antibody ratio	~3.5:1
Tumor-selective cleavable linker?	No
Evidence of bystander anti-tumor effect?	No

Trastuzumab emtansine (T-DM1)[5]

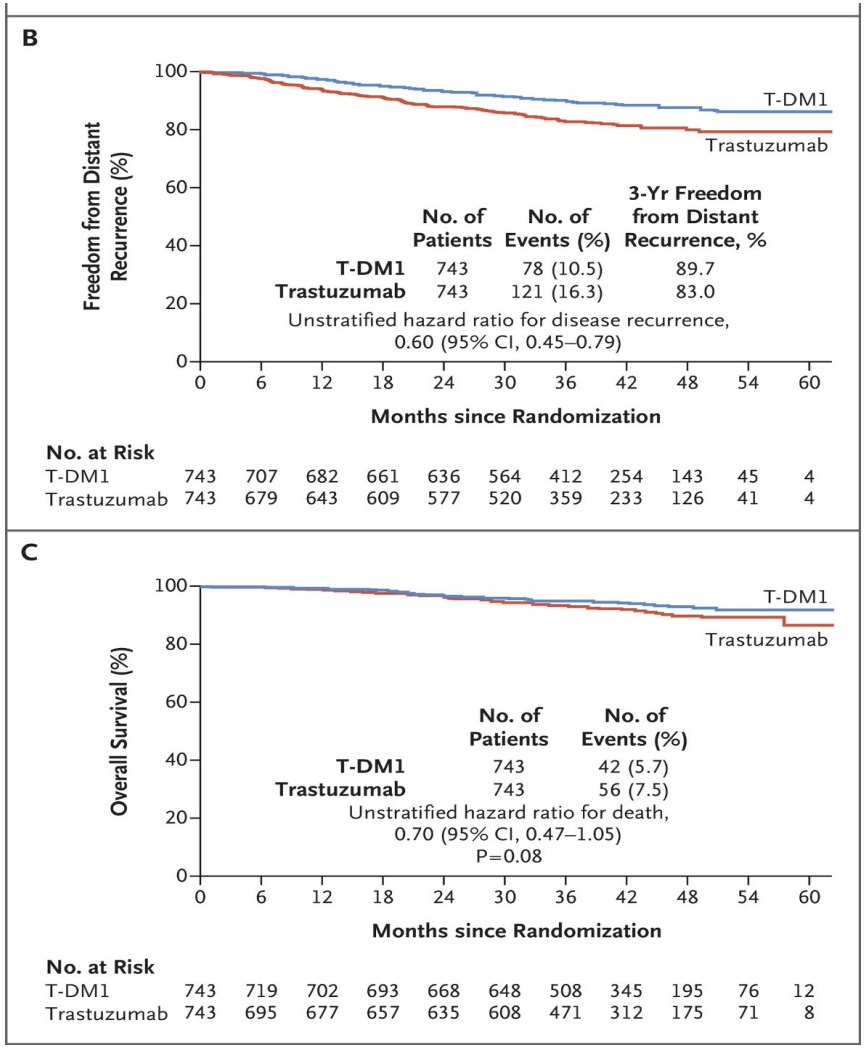


KATHERINE Trial, von Minckwitz, et al.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 14, 2019 VOL. 380 NO. 7

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer



Improvements in the Adjuvant Setting

APHINITY TRIAL

6 year follow up data:

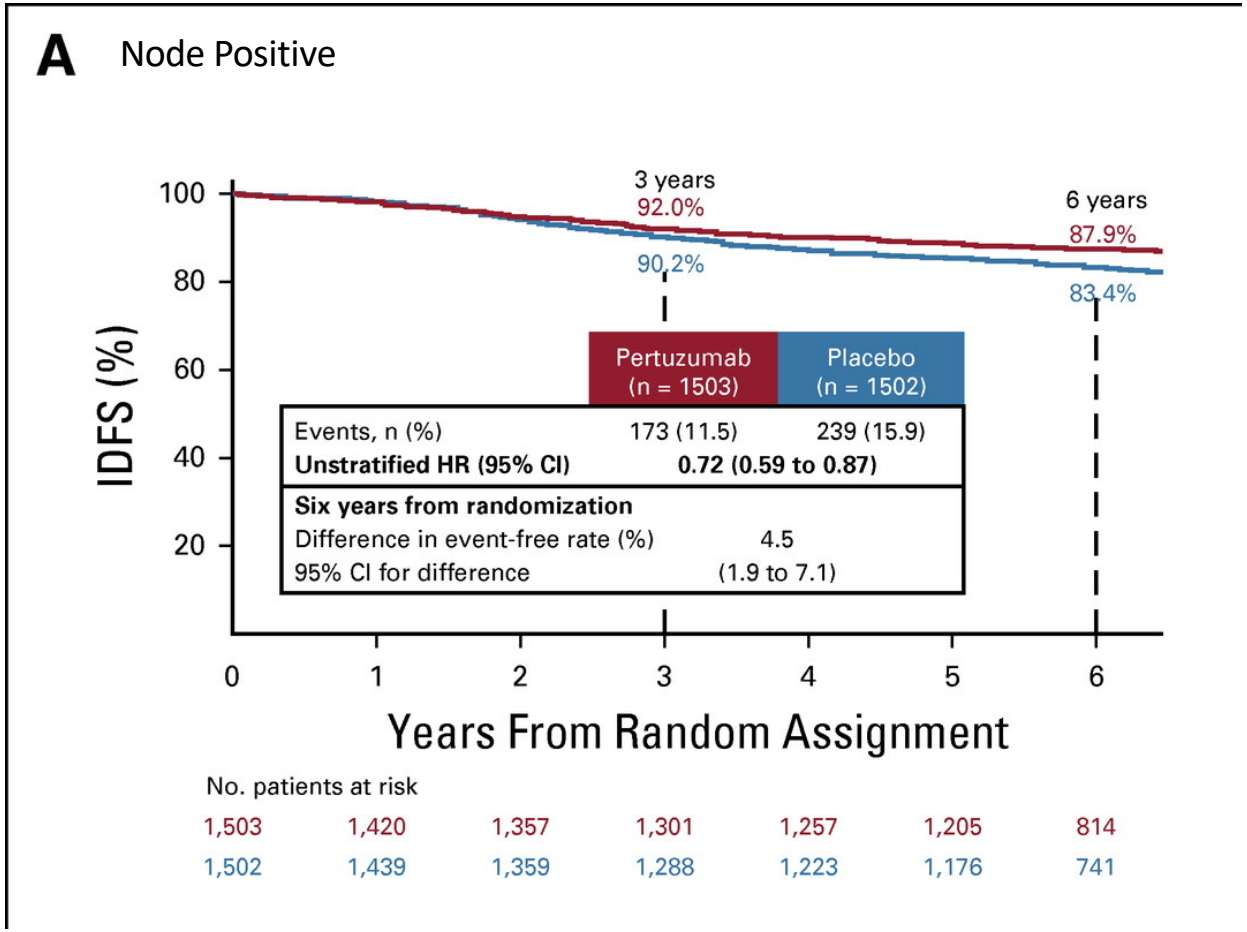
Overall IDFS 91% v 88%

Node pos IDFS 88% v 83%

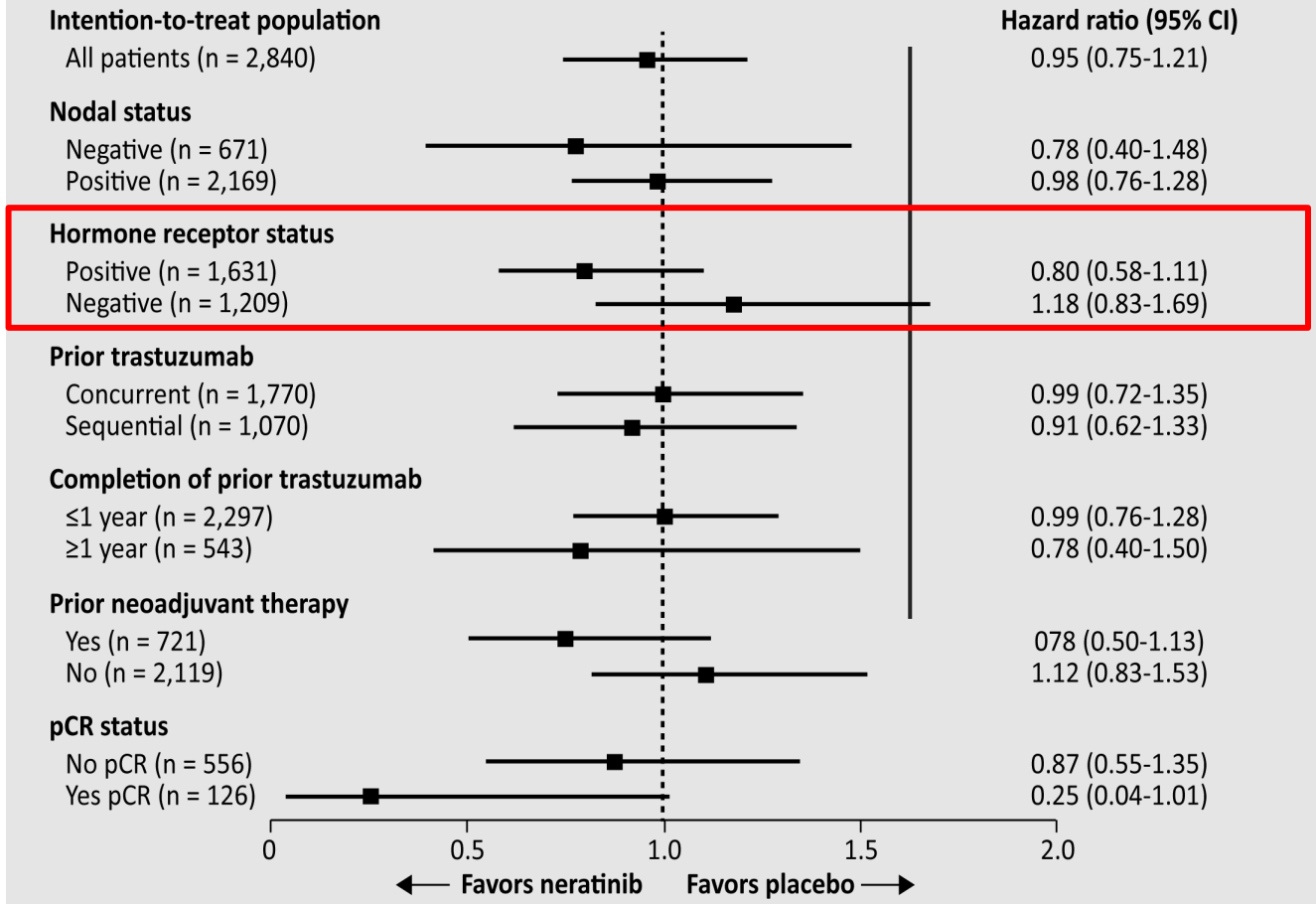
Both HR+ and HR- benefit:

3% gain and 2.5% gain respectively

Cardiac event rate <1%



ExteNET
Neratinib for Early Stage Her 2+ BC



HR+/≤ 1-year population (n=1334)

Absolute improvements seen:

- iDFS 5.1%, dDFS 4.7% , OS 2.1%

- 4 versus 12 CNS events for neratinib v placebo

- neoadjuvant/non-pCR population (n=295)
  - iDFS 7.4%, dDFS 7.0%, OS 9.1%

- neratinib is a pan-HER TKI

- unmitigated neratinib at recommended 240mg dosing has 40% incidence grade 3 diarrhea – SO MUST TITRATE!
- (CONTROL TRIAL)

Chan et al. Clin Breast Can 2021 doi.org/10.1016/j.dbc.2020.09.014

Summary of the Early Her2+ BC Field

NODE NEGATIVE

Adjuvant :

TH-> H

TCH->H

? TDM-1

Larger tumor [>2cm]:

Neoadjuvant TCHP -> HP

NODE POSITIVE

Neoadjuvant: TCHP or anthracycline based regimen

Adjuvant:

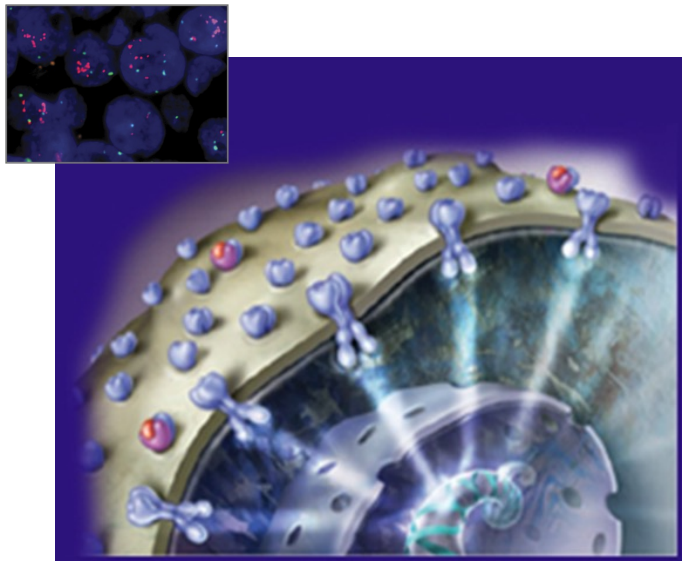
pCR yes: HP

pCR no: TDM-1

Option to add neratinib add if ER+ and high risk

Pregnancy: AC x 4 during 2 or 3rd trimester (stop by 36-37 weeks) then TH or THP postpartum

TODAY'S OPTIONS IN HER 2 TARGETED THERAPY FOR METASTATIC DISEASE

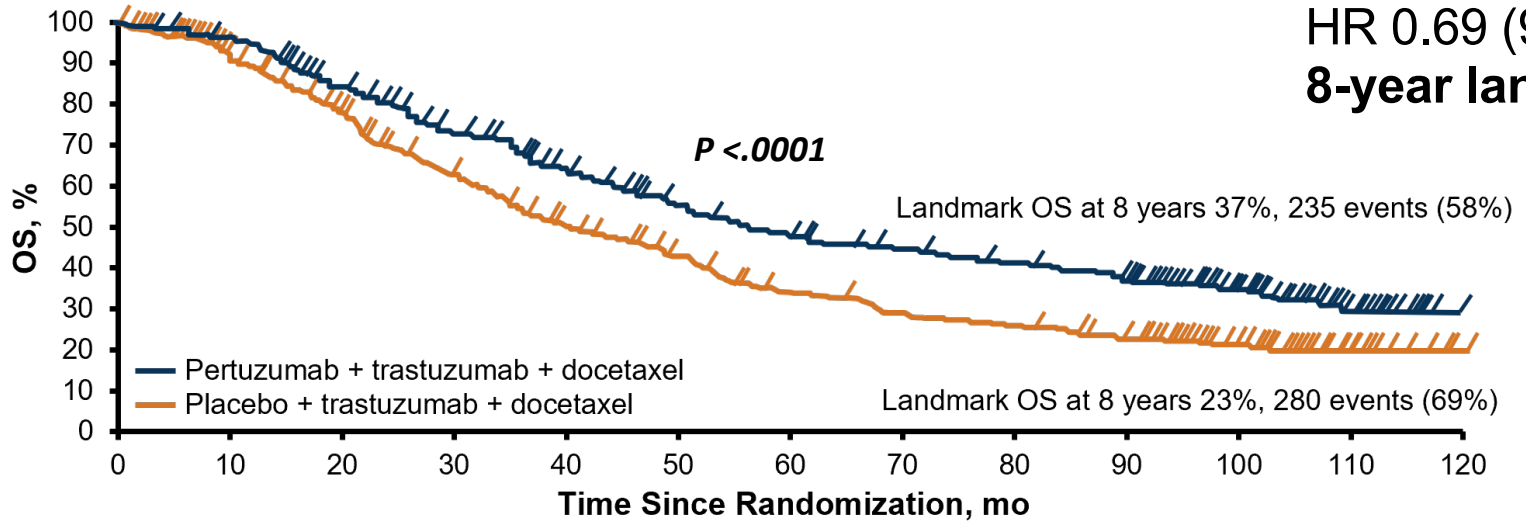


Overexpressed HER2

- trastuzumab
- pertuzumab
- ado-emtansine-trastuzumab [T-DM1]
- tucatinib
- trastuzumab-deruxtecan [T-DXd]
- margetuximab
- neratinib
- lapatinib

1st Line: Pertuzumab, Trastuzumab, and Docetaxel for HER2+ mBC (CLEOPATRA)

Overall Survival in Patients with Advanced HER2+ mBC



No. at Risk (number censored)

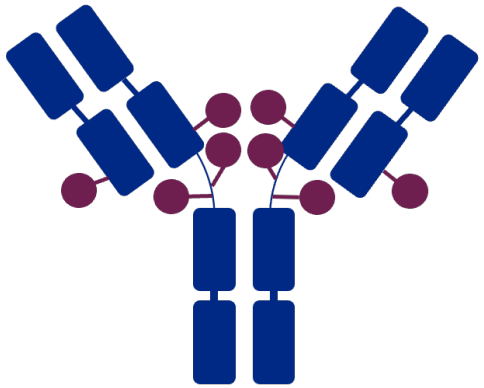
Pertuzumab	402 (0)	371 (14)	318 (23)	269 (32)	228 (41)	188 (48)	165 (50)	150 (54)	137 (56)	120 (59)	71 (102)	20 (147)	0 (167)
Placebo	406 (0)	350 (19)	289 (30)	230 (36)	181 (41)	149 (48)	115 (52)	96 (53)	88 (53)	75 (57)	44 (84)	11 (115)	1 (125)

Final OS analysis (median FU ~100 mo)
57.1 mo vs **40.8 mo**, + *Δ16.3mo*
HR 0.69 (95% CI, 0.58-0.82)
8-year landmark OS: 37% vs **23%**

Swain SM et al. *Lancet Oncol*. 2020;21:519-530.

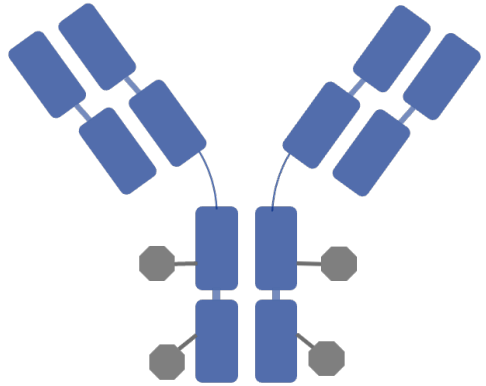
ADC Characteristic Differences Between T-DXd and T-DM1

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]



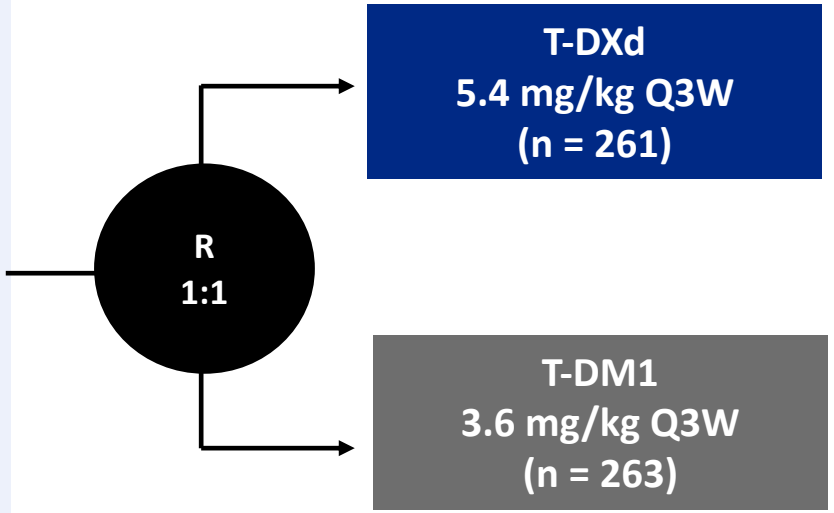
ADC, antibody-drug conjugate; MoA, mechanism of action.
[a]The clinical relevance of these features is under investigation.

1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85; 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108; 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42; 4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46; 5. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47.

DESTINY-Breast03: First Randomized Phase 3 Study of T-DXd

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

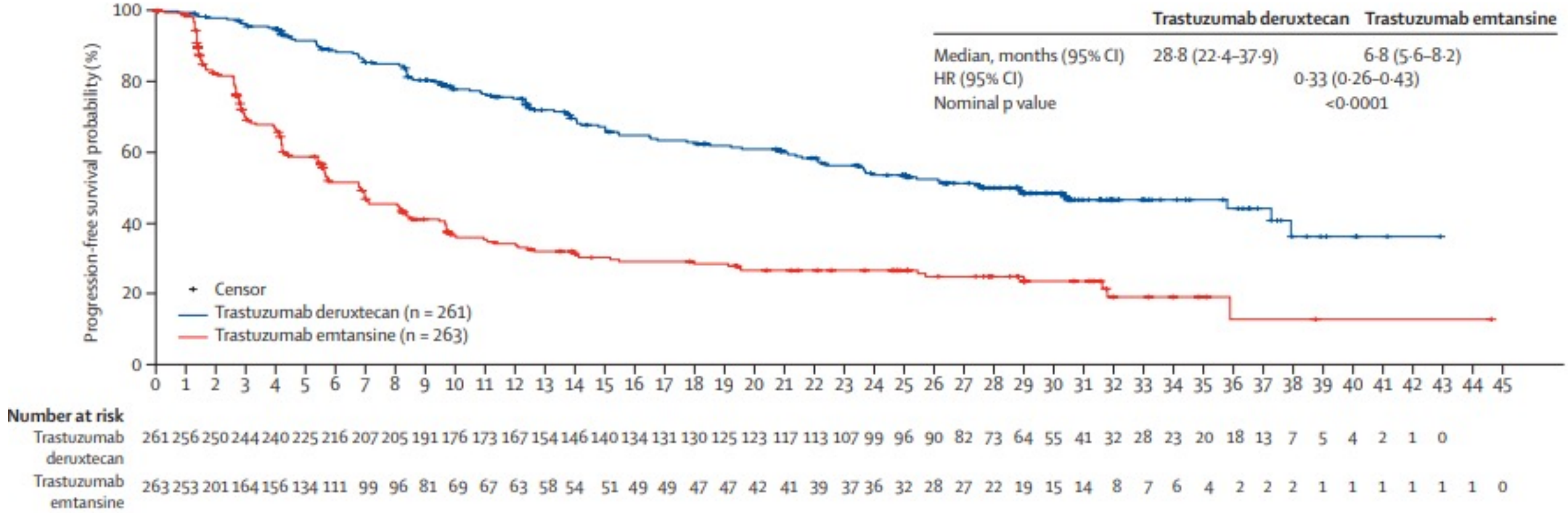
Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Prior therapy for MBC:
- 100% received prior trastuzumab
- 60% received prior pertuzumab
- 16% received HER2 TKI

[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation.
[b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

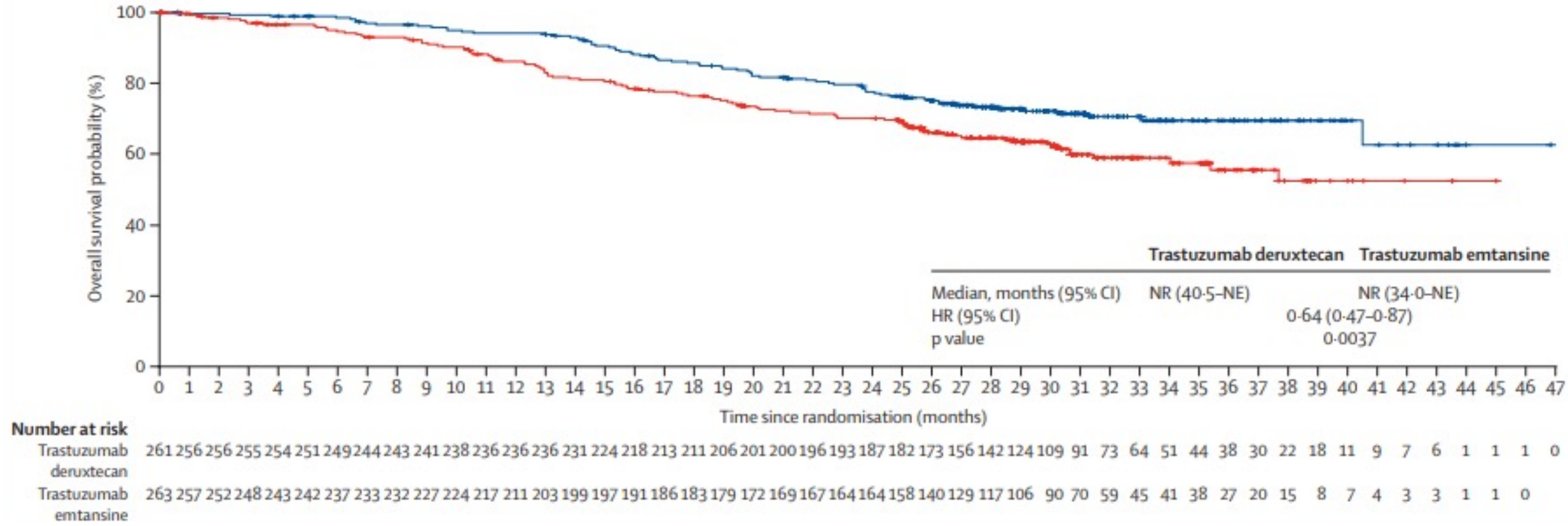
Cortés J et al. ESMO 2021. Abstract LBA1.

DESTINY-Breast03: Updated PFS



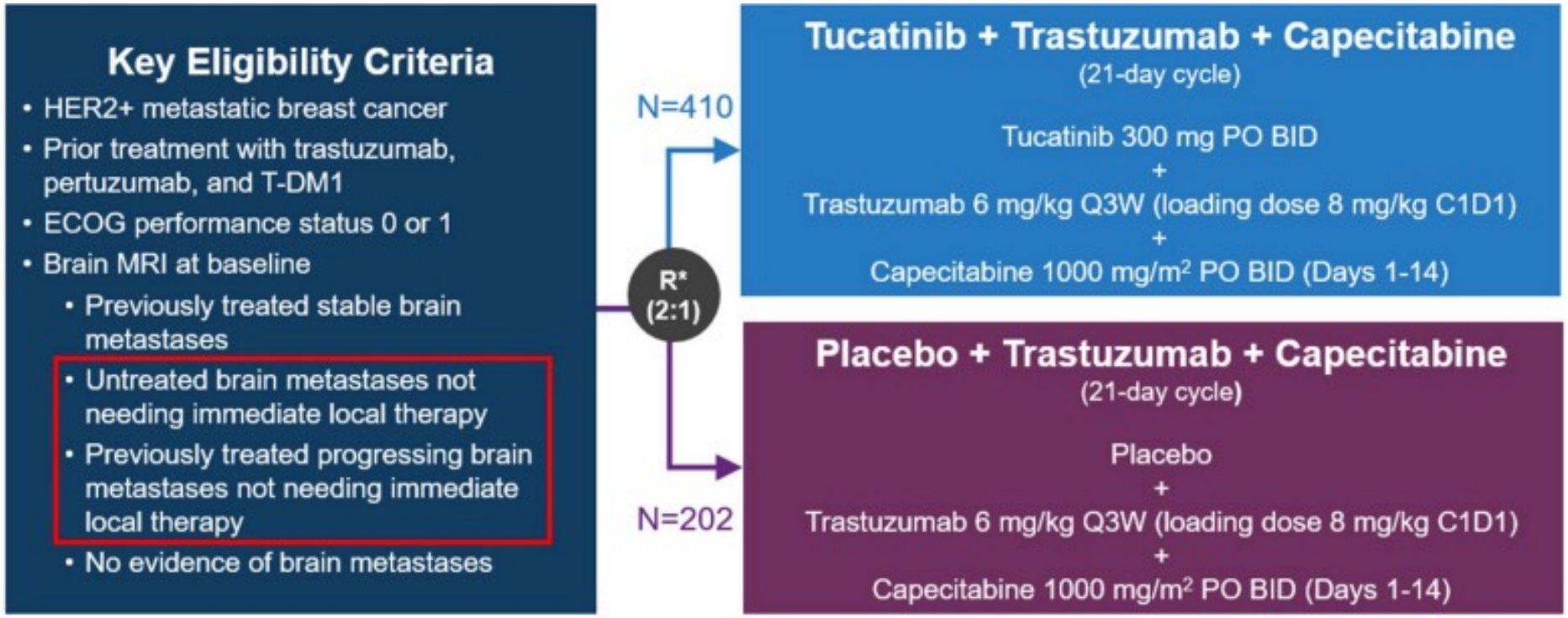
Hurvitz S et al. *Lancet.* 2023;401(10371):105-117.

DESTINY-Breast03: Updated OS



Hurvitz S et al. *Lancet.* 2023;401(10371):105-117.

HER2CLIMB Trial – Study Design



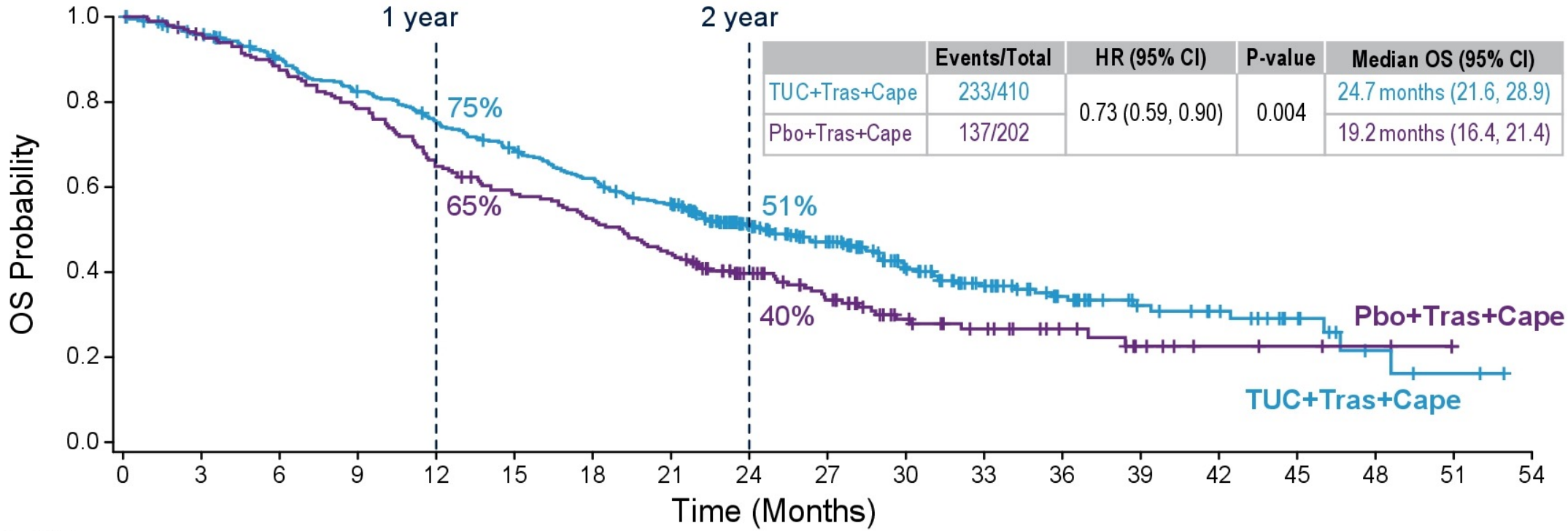
Primary endpoint:
- PFS in all patients

Secondary endpoints:
- PFS in patients with brain metastases*
- OS in all patients

***Brain metastases in 48% of patients**
- Untreated = 22%
- Treated, progressing = 18%

Murthy R et al. *Lancet Oncol.* 2018;19(7):880-888.

HER2CLIMB Trial: Updated OS



	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	233/410	0.73 (0.59, 0.90)	0.004	24.7 months (21.6, 28.9)
Pbo+Tras+Cape	137/202			19.2 months (16.4, 21.4)

Subjects at Risk

TUC+Tras+Cape	410	387	356	325	295	268	241	214	153	122	81	56	38	24	19	11	4	2	0
Pbo+Tras+Cape	202	191	174	156	129	114	103	87	63	47	28	21	14	8	4	3	2	0	0

a. Median overall study follow-up: 29.6 months

Curigliano G et al. ASCO 2021. Abstract 1043.

HER2CLIMB-02 Study Design

- HER2+ LA/MBC with progression after trastuzumab and taxane in any setting[a]
- ECOG PS ≤1
- Previously treated stable, progressing, or untreated brain metastases not requiring immediate local therapy

N≈460

R 1:1

Stratification factors:
- Line of treatment for metastatic disease (1L vs other)
- Hormone receptor status (positive vs negative)
- Presence or history of brain metastases (yes vs no)
- ECOG PS (0 vs 1)

T-DM1 + Tucatinib

T-DM1 3.6 mg/kg IV and tucatinib 300 mg PO BID

T-DM1 + Placebo

T-DM1 3.6 mg/kg IV and Placebo PO BID

Outcomes

Primary
- PFS by investigator assessment per RECIST v1.1

Key Secondary (hierarchical)
- OS
- PFS in patients with brain metastases
- cORR per RECIST v1.1
- OS in patients with brain metastases

The primary analysis for PFS was planned after ≈331 PFS events to provide 90% power for hazard ratio of 0.7 at two-sided alpha level of 0.05. The first of two interim analysis for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive.[b]

NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Accessed Oct 5, 2023.
a Patients who received prior tucatinib, afatinib, T-DXd, or any investigational anti-HER2, anti-EGFR, or HER2 TKIs were not eligible. Patients who received lapatinib and neratinib were not eligible if the drugs were received within 12 months of starting study treatment, and patients who received pyrotinib for recurrent or metastatic breast cancer were not eligible. These patients were eligible if the drugs were given for ≤21 days and were discontinued for reasons other than disease progression or severe toxicity.
b Subsequent OS analyses are planned upon 80% and 100% of required events for the final OS analysis.
1L, first-line; BID, twice daily; cORR, confirmed objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; LA/MBC, locally advanced or metastatic breast cancer; OS, overall survival; PFS, progression-free survival; PO, orally; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKIs, tyrosine kinase inhibitors.
Date of data cutoff: Jun 29, 2023. Patients were enrolled from Oct 8, 2019, to Jun 16, 2022.

Demographics and Baseline Characteristics

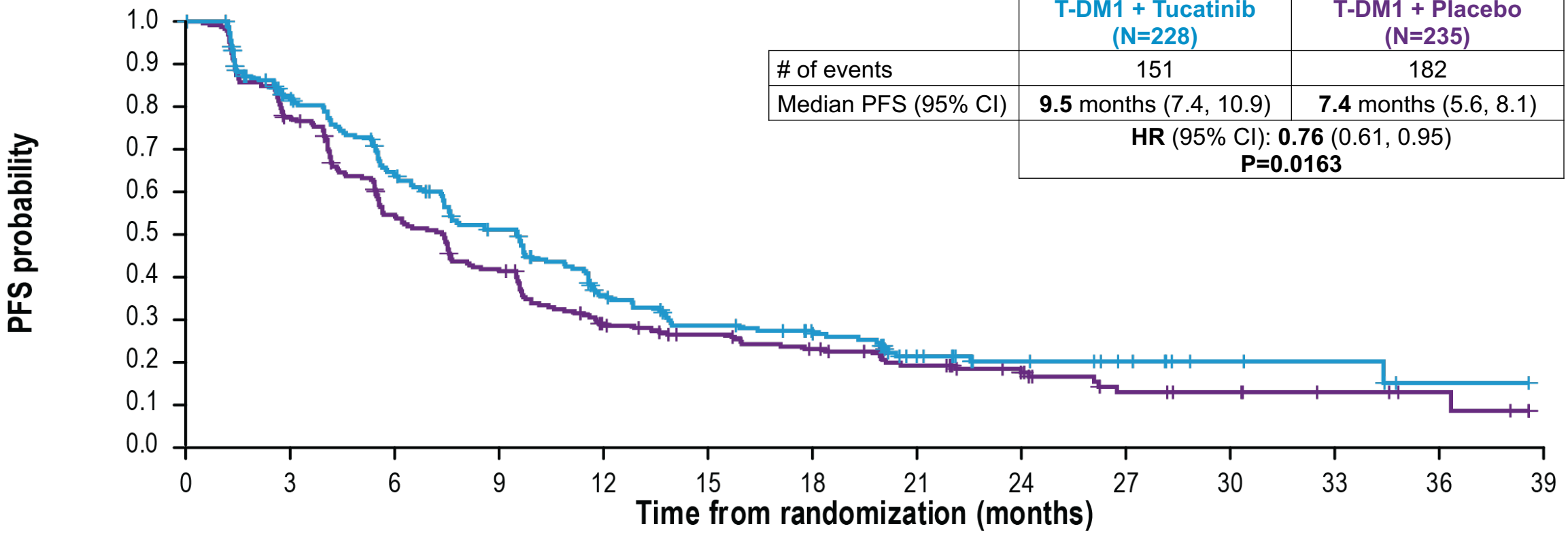
	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
Median age, years (range)	55.0 (26-83)	53.0 (27-82)
Female sex, n (%)	226 (99.1)	235 (100)
Geographic region, n (%)		
North America	105 (46.1)	93 (39.6)
Europe/Israel	53 (23.2)	77 (32.8)
Asia-Pacific	70 (30.7)	65 (27.7)
Hormone-receptor status, n (%)		
Positive	137 (60.1)	140 (59.6)
Negative	91 (39.9)	95 (40.4)
ECOG performance status score, n (%)		
0	137 (60.1)	141 (60.0)
1	91 (39.9)	94 (40.0)

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
Presence or history of brain metastases, n (%)		
Yes	99 (43.4)	105 (44.7)
Active	50 (21.9)	57 (24.3)
Treated stable	49 (21.5)	48 (20.4)
No[a]	129 (56.6)	130 (55.3)
Stage at initial diagnosis, n (%)[b]		
0-III	120 (52.6)	130 (55.3)
IV	103 (45.2)	98 (41.7)

a Includes 2 patients with missing brain metastases data.
b Five patients in T-DM1 + Tucatinib arm and 7 patients in T-DM1 + Placebo arm had unknown stage.
ECOG, Eastern Cooperative Oncology Group; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

Progression-Free Survival

	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	151	182
Median PFS (95% CI)	**9.5** months (7.4, 10.9)	**7.4** months (5.6, 8.1)
	HR (95% CI): **0.76** (0.61, 0.95) **P=0.0163**	



Patients at risk

T-DM1 + Tucatinib	228	165	126	96	62	47	40	22	14	10	5	4	1	0
T-DM1 + Placebo	235	177	120	91	58	48	40	29	19	10	8	5	3	0

HR, hazard ratio; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Date of data cutoff: Jun 29, 2023.

HER2 Overexpressed/Amplified MBC

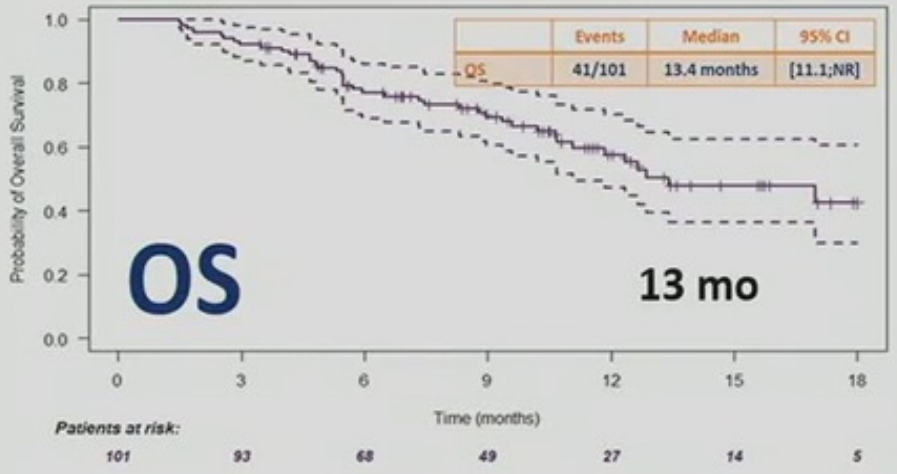
Tucatinib + TC after T-DXd

- Design:
  - Retrospective study involving 12 French comprehensive cancer centers
- Main Inclusion criteria:
  - HER2+ MBC treated with TTC between 08/2020 and 12/2022
  - Pretreatment with T-DXd (stopped for progression or toxicity)

- Patient characteristics:
  - Median 4 prior LOT for metastatic disease
  - 93% had prior T-DM1 as well

Median Follow-up: 11.6 months [10.5-13.4]

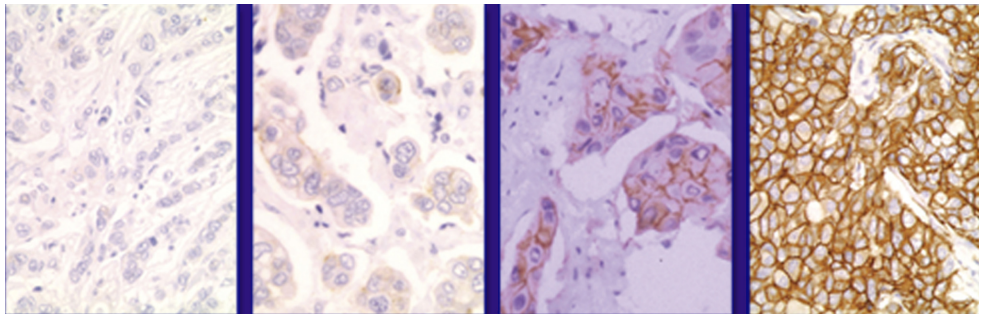
Estimated PFS at 6 months (95% CI)	
33.1%	[24.8;44.3]
Estimated PFS at 12 months (95% CI)	
11.9%	[6.4;22.1]



Estimated OS at 6 months (95% CI)	
77.0%	[69.0;86.0]
Estimated OS at 12 months (95% CI)	
57.5%	[47.2;66.1]

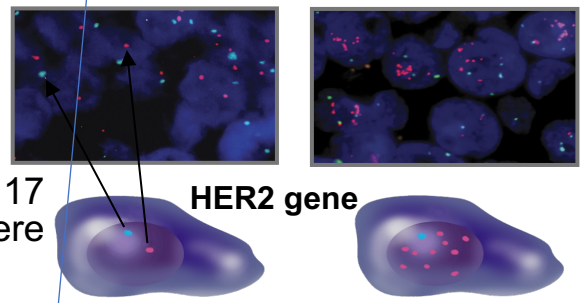
Frenel JS et al. ASCO 2023. Abstract 1014.

HER2 Protein Overexpression and Amplification for Clinical Discrimination



IHC 0 IHC I+ IHC 2+ IHC 3+

Her 2 negative



HER2-normal Ratio <2.0

HER2-amplified Ratio ≥2.0

Her 2 Positive

Treatment pathway follows the ER status

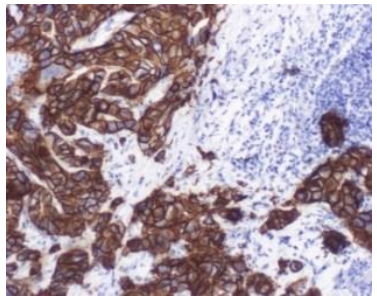
Her 2 Low treatment pathway in MBC

Treatment driven down the Her 2 pathway

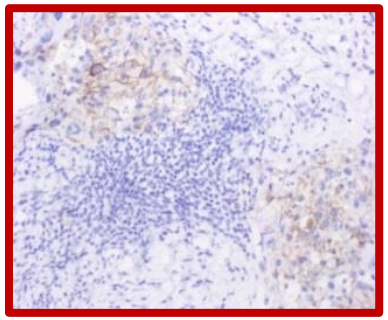
Prevalence of HER2-low Breast Cancer (IHC 1+/2+, FISH negative)

HER2 IHC examples

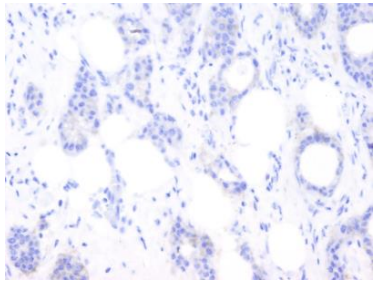
HER2+

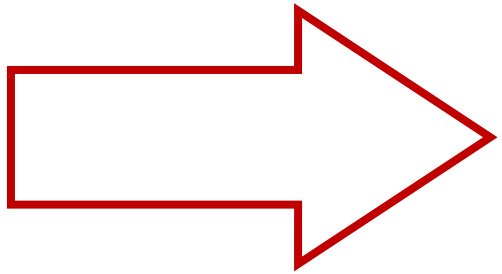


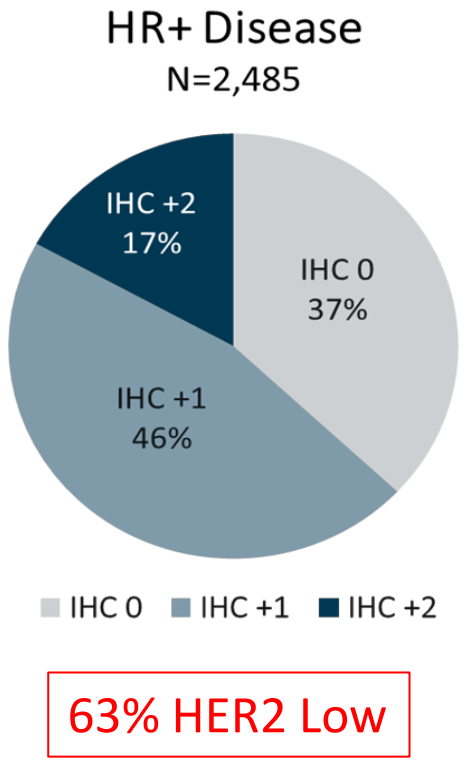
HER2-low



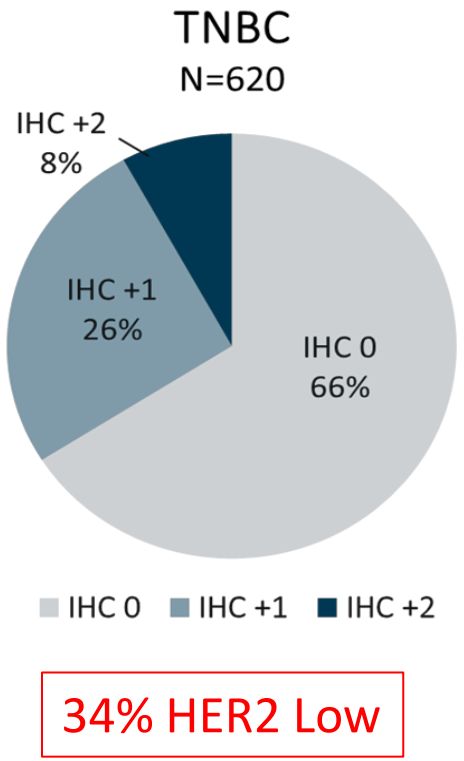
HER2-







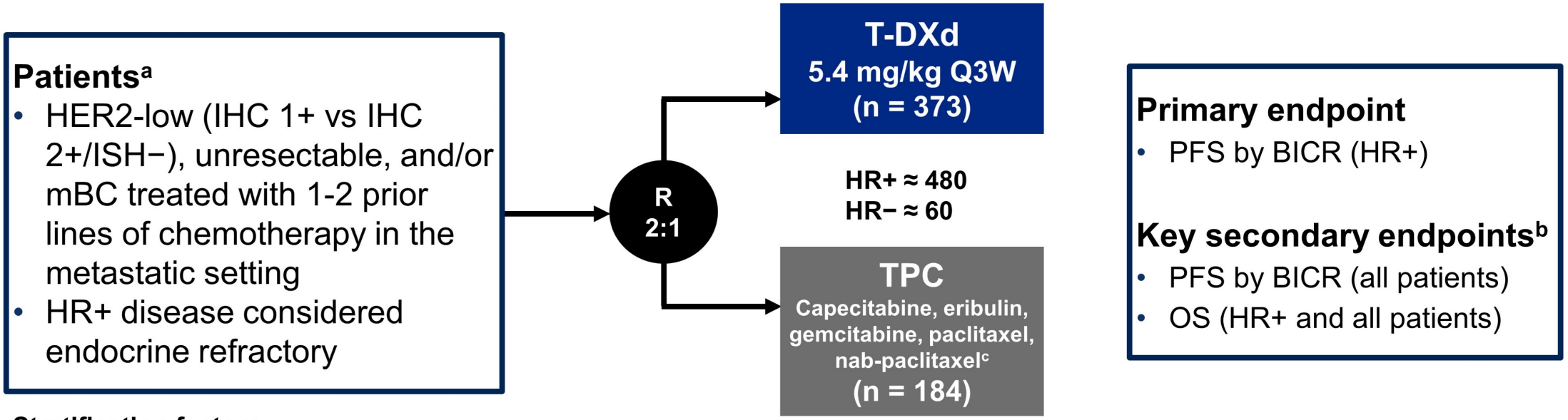
63% HER2 Low



34% HER2 Low

Schettini F et al. *NPJ Breast Cancer.* 2021;7(1):1.

DESTINY-Breast04: Randomized, Phase 3 Study of Trastuzumab Deruxtecan for HER2-low mBC



Stratification factors

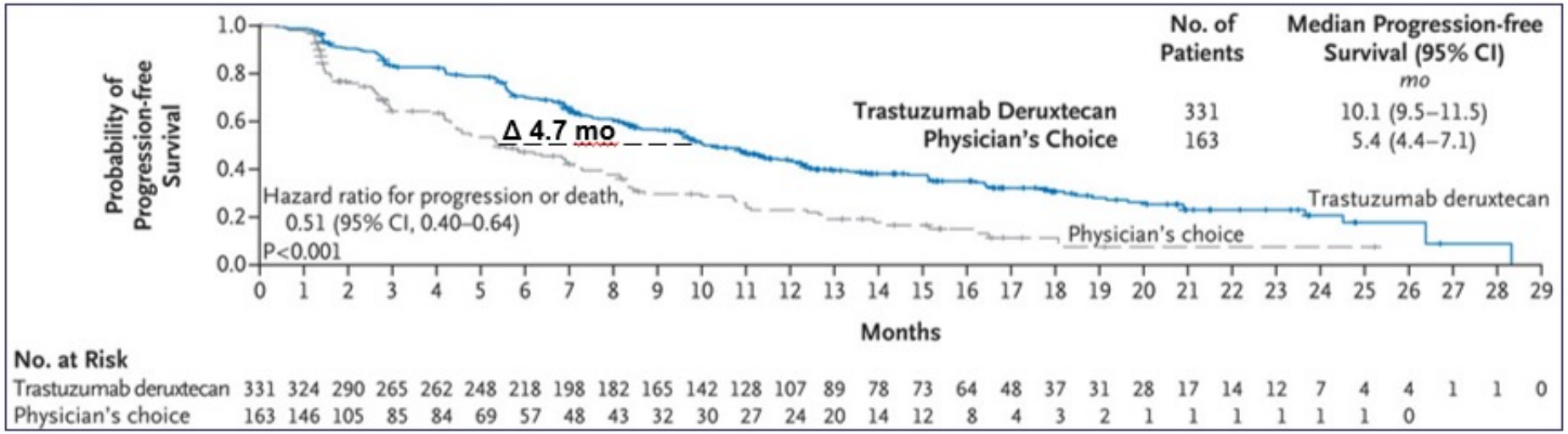
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

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.

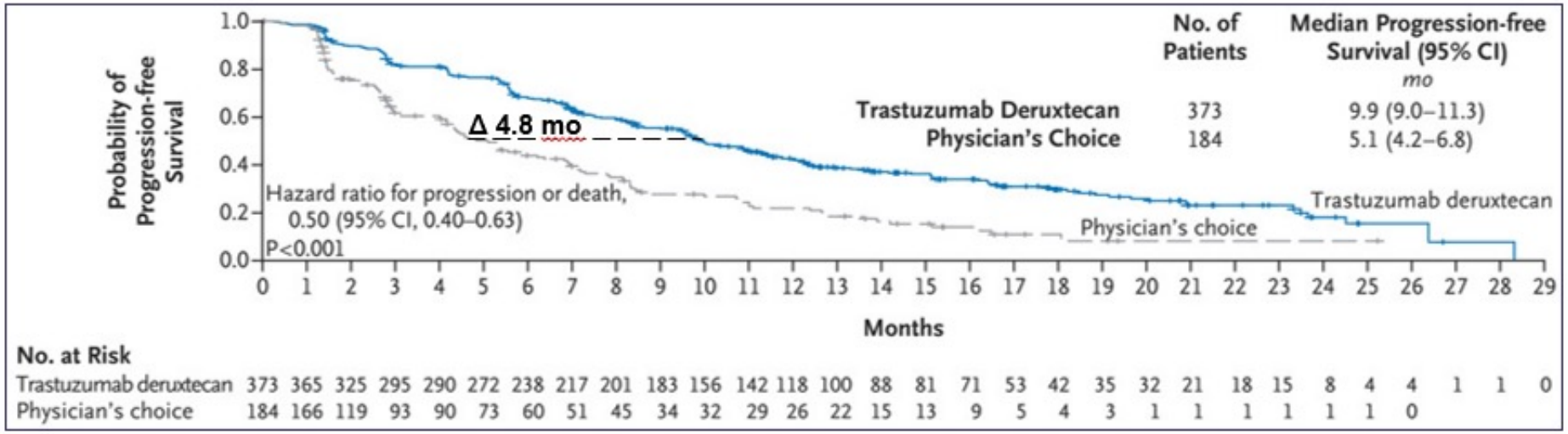
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate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

DESTINY-Breast04: Primary Endpoint – PFS

HR+ Patients



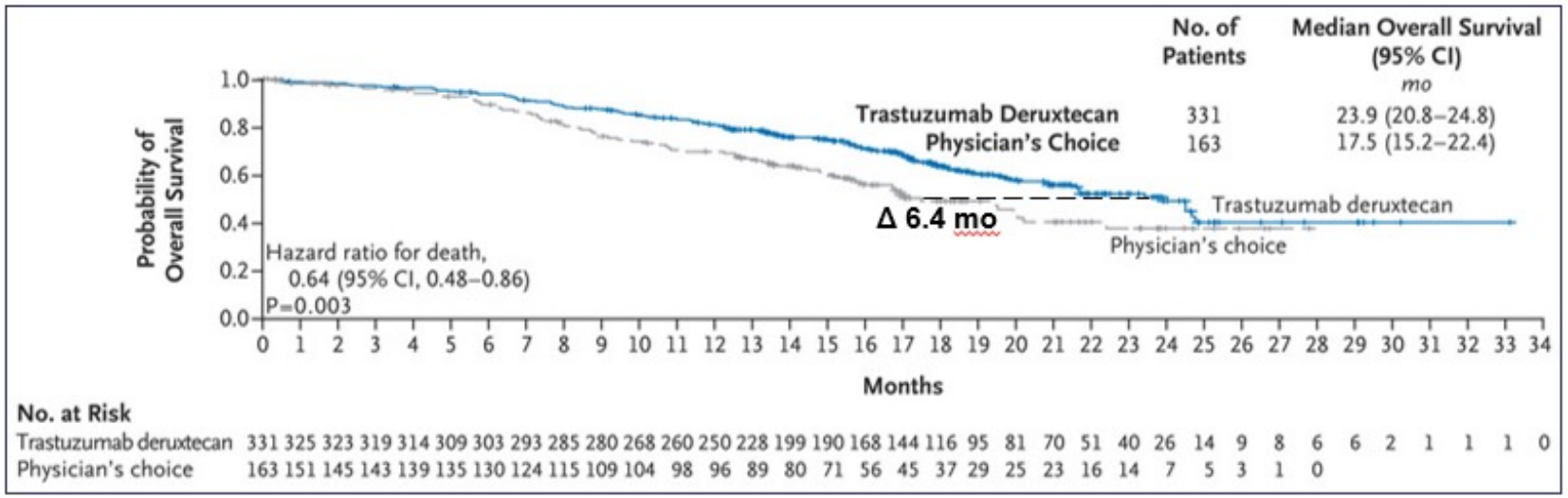
All Patients



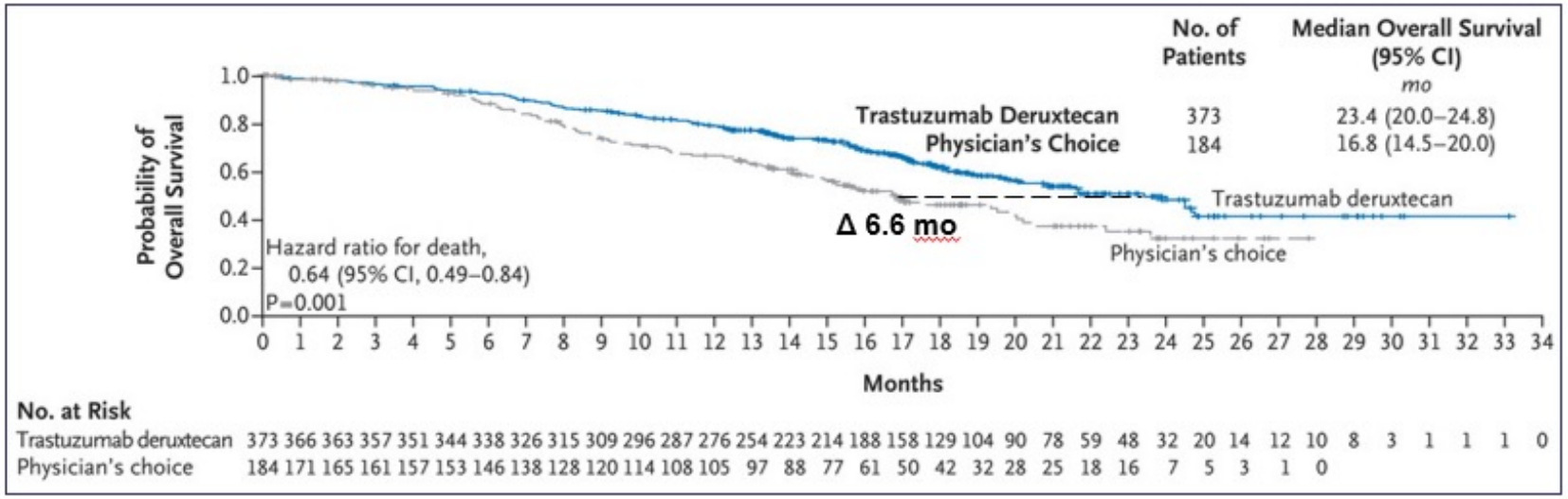
Modi S et al. *N Engl J Med.* 2022;387(1):9-20.

DESTINY-Breast04: Secondary Endpoint – OS

HR+ Patients

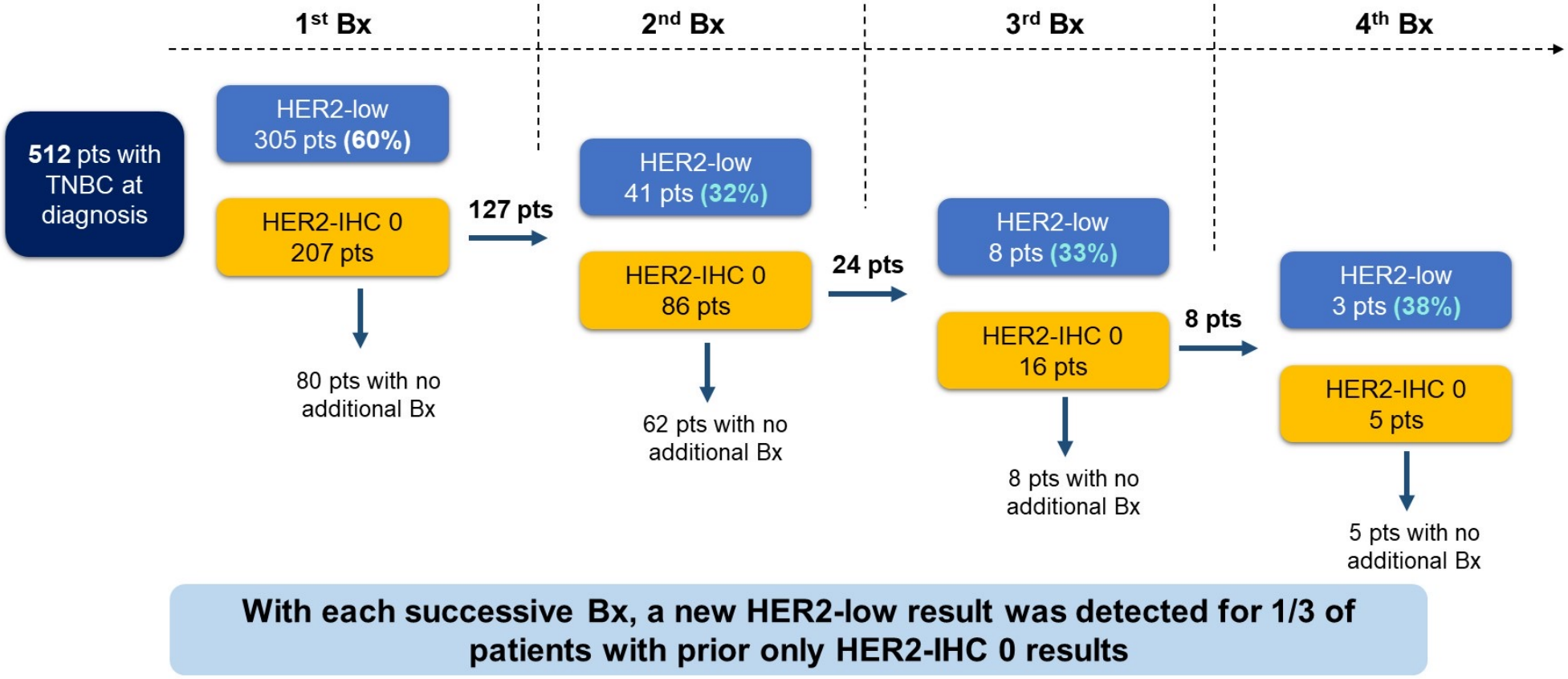


All Patients



Modi S et al. *N Engl J Med.* 2022;387(1):9-20.

HER2-Low Expression is Dynamic in Breast Cancer: Impact of Repeat Biopsies in TNBC



With each successive Bx, a new HER2-low result was detected for 1/3 of patients with prior only HER2-IHC 0 results

Bar Y et al. ASCO 2023. Abstract 1005.

HER 2 activating mutations (ERBB2)

- oncogenic drivers in a subset of breast and other cancers[1,2]
- HER2 mutations typically occur in the absence of HER2 amplification[3,4]
- more common in invasive lobular breast cancer[5,6]
- associated with poor prognosis[5,6]
- 5% of endocrine resistant metastatic breast cancers[7]
- implicated in resistance to HER2 inhibitors in HER2-amplified breast cancers [8,9]
- can be targeted with HER2 tyrosine kinase inhibitors[10]
- **Approximately 30% of HER2-mutant MBC respond to neratinib**

1 Bose et al.,2013
2 Hanker et al., 2017
3 Deniziaut et al., 2016
4 Desmedt et al., 2016
5 Ping et al., 2016
6 Kurozumi et al., 2020
7 Razavi et al., 2018
8 Cocco et al., 2018
9 Xu et al.,2017
10 Hyman et al.,2018

Thank you!