Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC)

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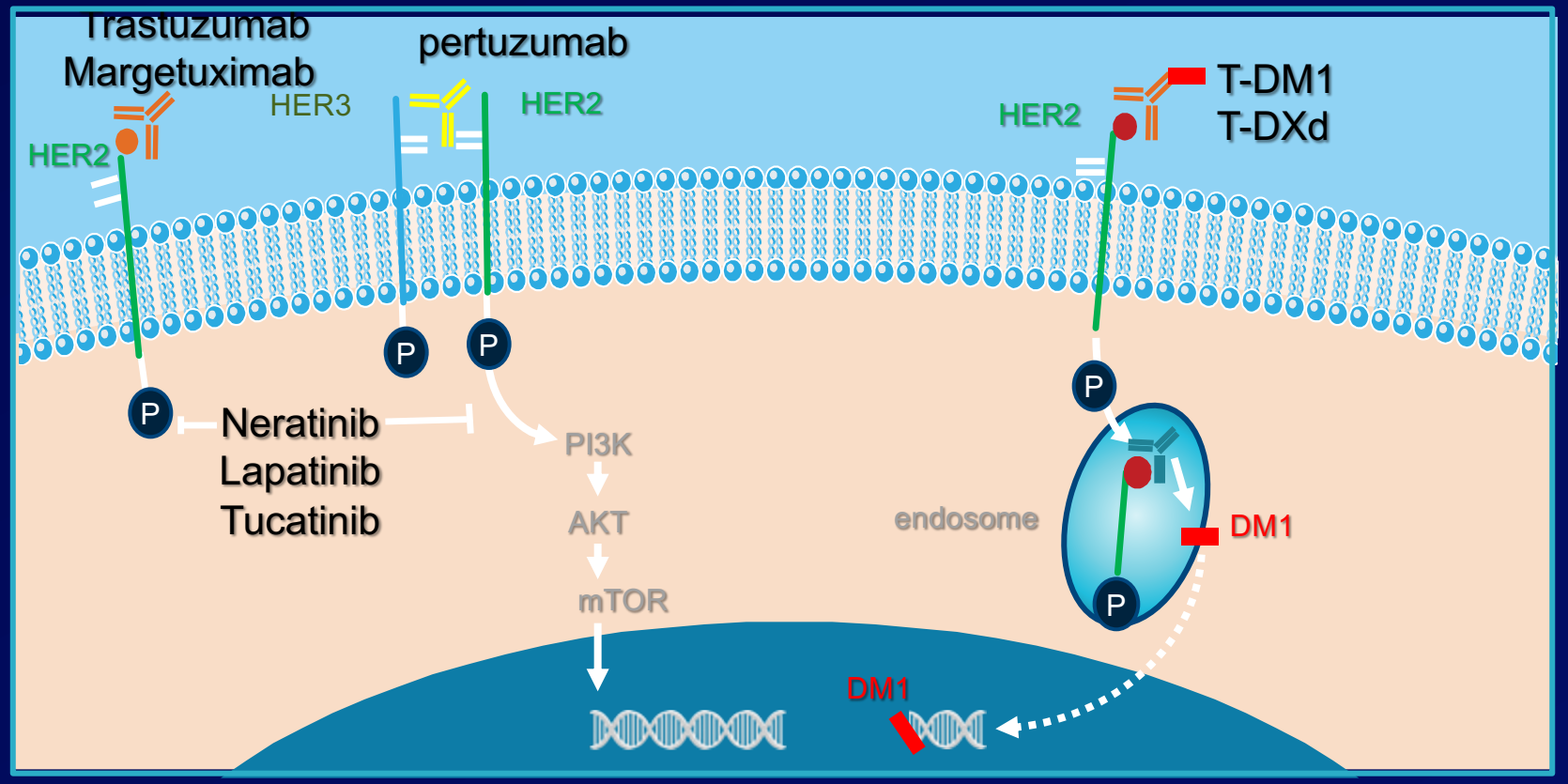
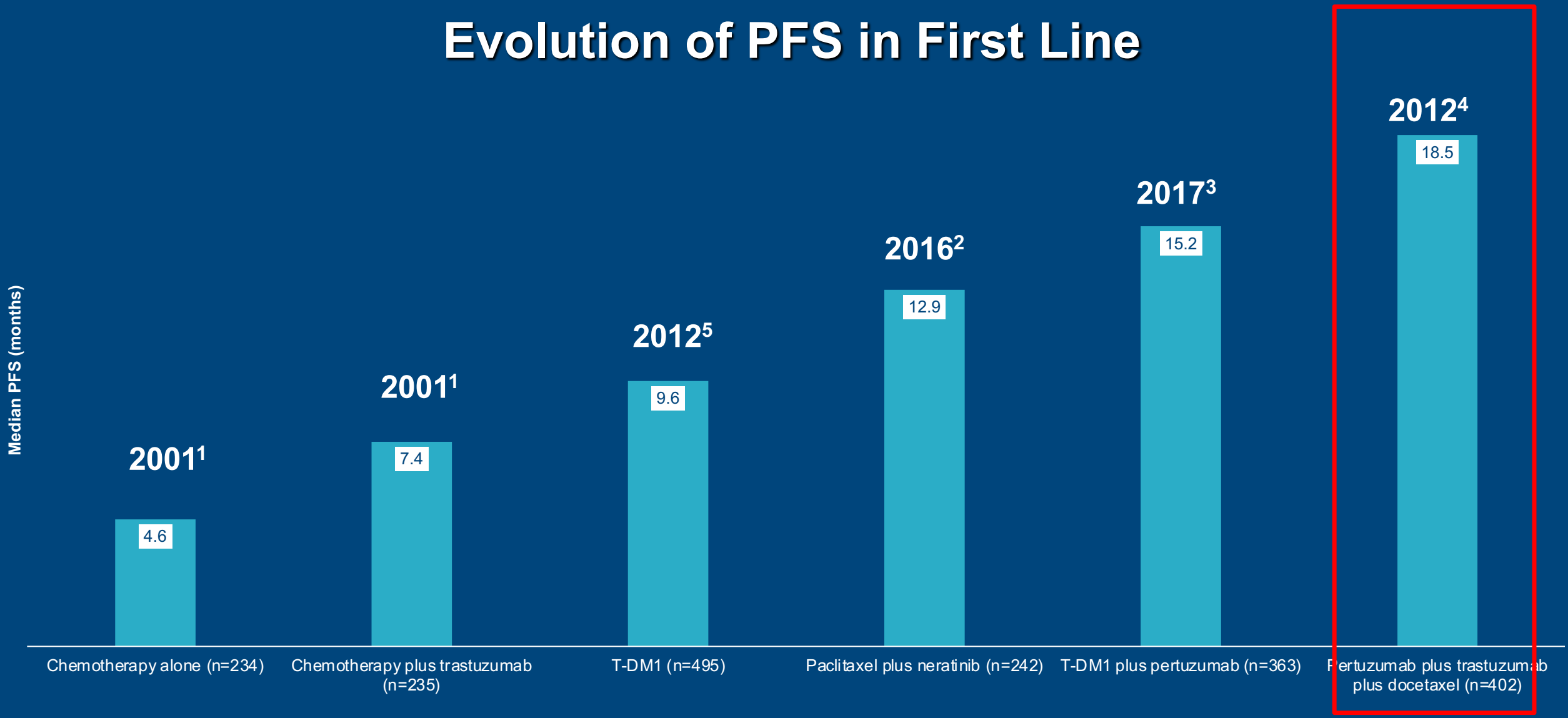
We have an expanding armamentarium of agents for HER2+ breast cancer: Which regimen for which patients?



PI3K = phosphoinositide 3-kinase; AKT = a serine/threonine kinase; mTOR = mammalian target of rapamycin.

Adapted from Gajria D, Chandarlapaty S. *Expert Rev Anticancer Ther*. 2011;11:263-275.

Evolution of PFS in First Line



1L=first line; HER2=human epidermal growth factor receptor 2; PFS=progression-free survival; T-DM1=ado-trastuzumab emtansine.

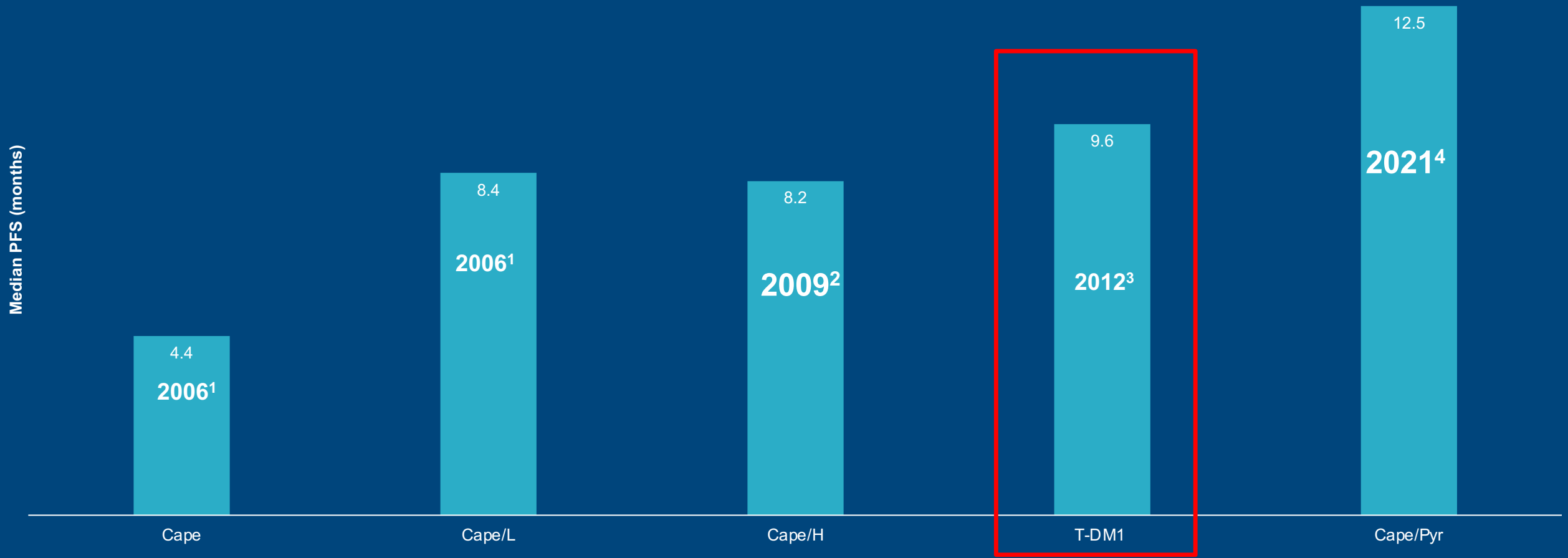
Adapted from: 1. Slamon DJ, et al. *N Engl J Med*. 2001;344:783–792; 2. Awada A, et al. *JAMA Oncol.* 2016;2:1557–1564; 3. Perez EA, et al. *J Clin Oncol.* 2017;35:141–148; 4. Baselga J, et al. *N Engl J Med.* 2012;366:109–119; 5. Verma S, et al. N Engl J Med. 2012;367(19):1783–1791

NCCN v1.2022 Recommendations Advanced HER2+ Disease

Setting	Regimen	Evidence Level
First Line	**Docetaxel/Trastuzumab/Pertuzumab (preferred)** *(Paclitaxel may be used in place of docetaxel, level 2A)*	1
Second Line		
Third Line and Beyond (optimal sequence unknown)		

Second Line Therapy (after trastuzumab/taxane)

Evolution of PFS after trastuzumab/taxane



Cape=capecitabine; DCO=data cut-off; H=trastuzumab; L=lapatinib; (m)PFS=(median) progression-free survival; Pyr=pyrotinib; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan.

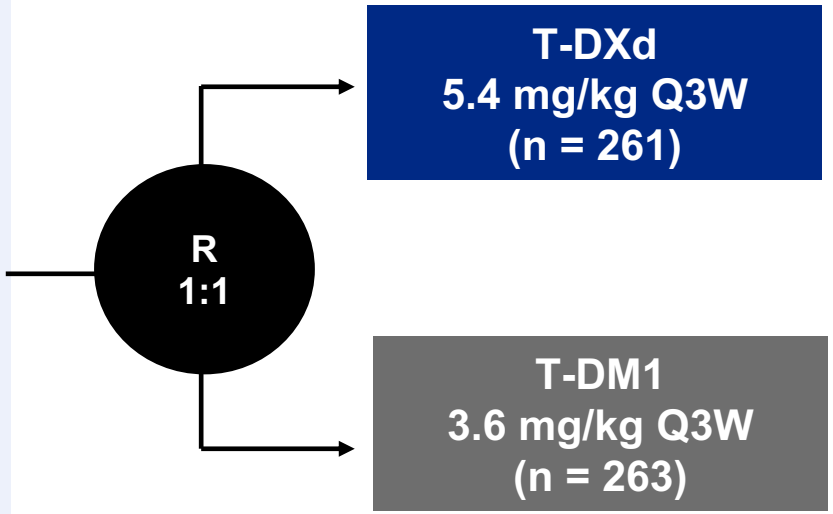
1. Geyer C, et al. *N Engl J Med*. 2006;355:2733–2743; 2. Von Minckwitz G, et al. *J Clin Oncol*. 2009;27:1999–2006; 3. Verma S, et al. *N Engl J Med*. 2012;367:1783–1791; 4. Xu B, et al. *Lancet Oncol*. 2021;22:351–360;

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

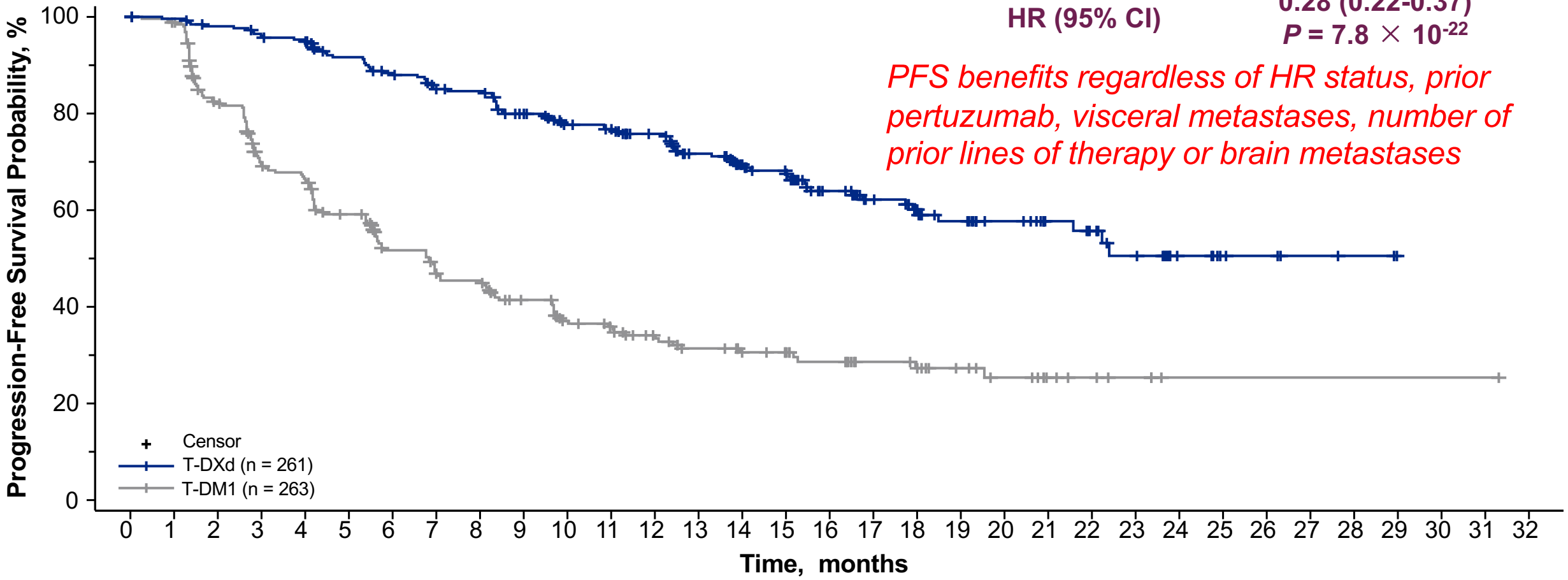
Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

22% history of brain metastases
70% history of visceral metastases
48% 1 prior line therapy
60% prior pertuzumab

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 × 10^{-22}**	

PFS benefits regardless of HR status, prior pertuzumab, visceral metastases, number of prior lines of therapy or brain metastases



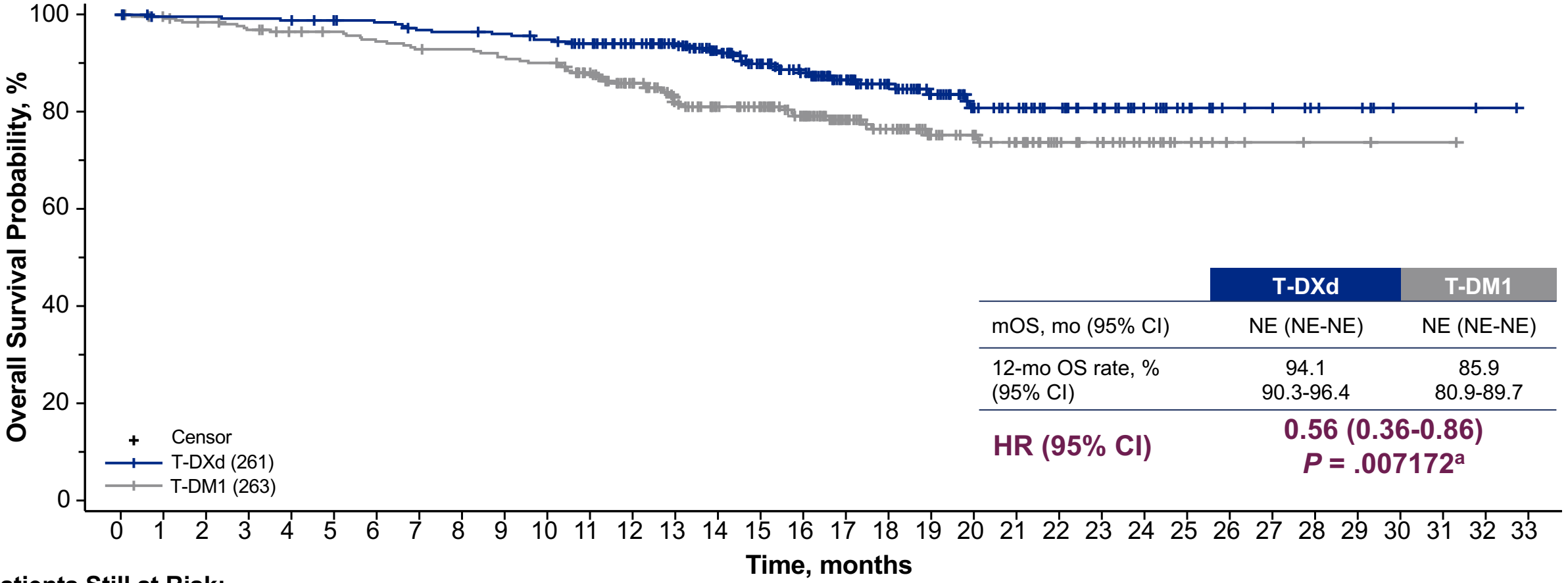
Patients Still at Risk:

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

2021 ESMO congress

Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and for T-DM1 was 13.9 months (range, 11.8-15.1)
HR, hazard ratio; INV, investigator; mo, month; NE, not estimable; NR, not reached.

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]**	

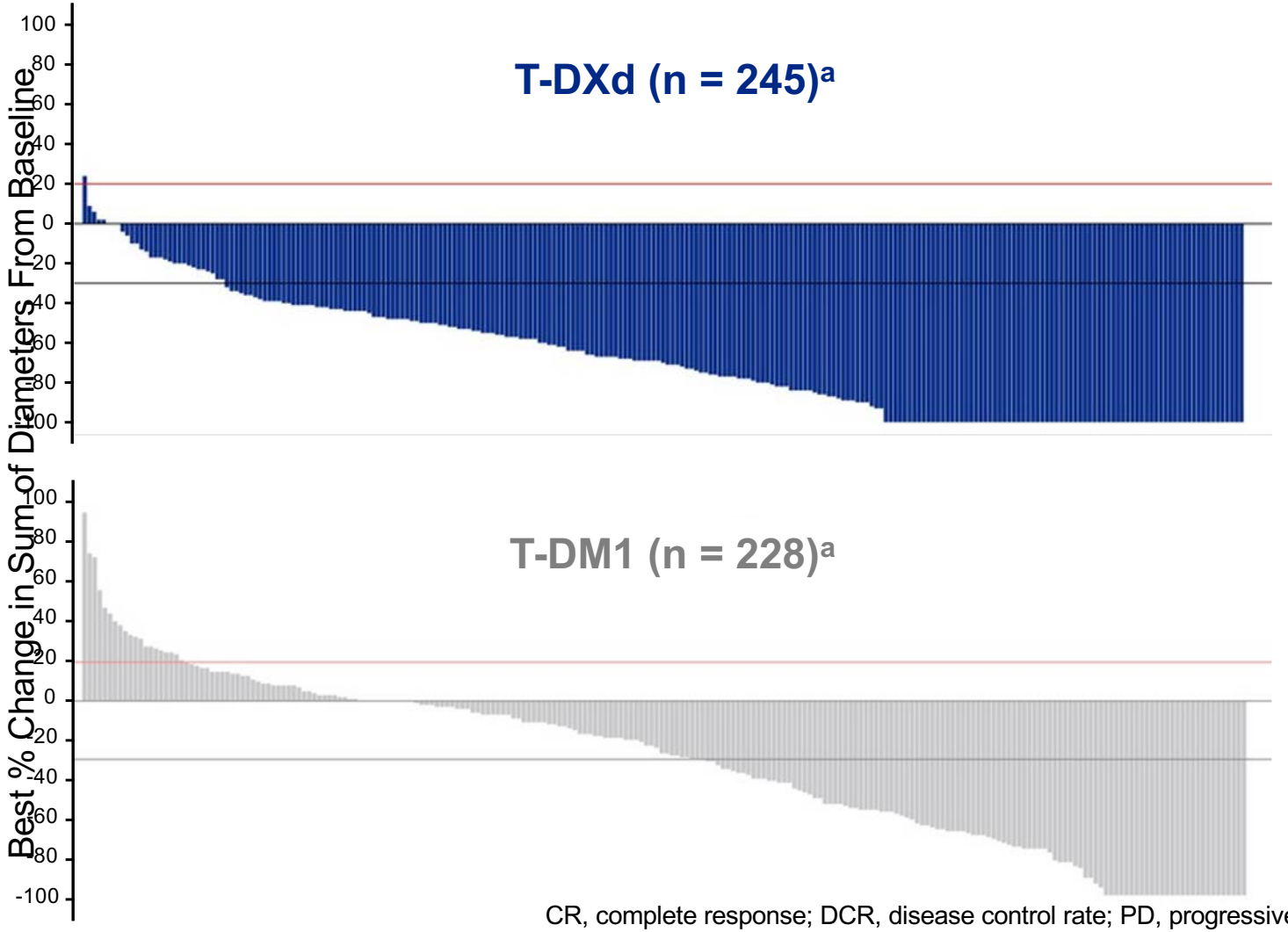
Patients Still at Risk:

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*<0.000265

Confirmed ORR and Best Overall Response



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b]	208 **(79.7)**	90 **(34.2)**
[95% CI]	[74.3-84.4]	[28.5-40.3]
	P < .0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Only subjects with measurable disease at baseline and at least one postbaseline target lesion assessment are included. [b]Based on BICR.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.

2021 ESMO congress

Cortes J et al ESMO 2021

Drug-related TEAEs in ≥20% of Patients

System Organ Class Preferred term, n (%)	T-DXd (n = 257)		T-DM1 (n = 261)	
	Any Grade	Grade ≥3	Any Grade	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	93 (36.2)	1 (0.4)	6 (2.3)	0

Most drug-related TEAEs were gastrointestinal or hematological in nature

Adverse events were managed according to the protocol.

[a]This category includes the preferred terms neutrophil count decreased and neutropenia. [b]This category includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [c]This category includes the preferred terms white blood cell count decreased and leukopenia. [d]This category includes platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms fatigue, asthenia, and malaise.

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)

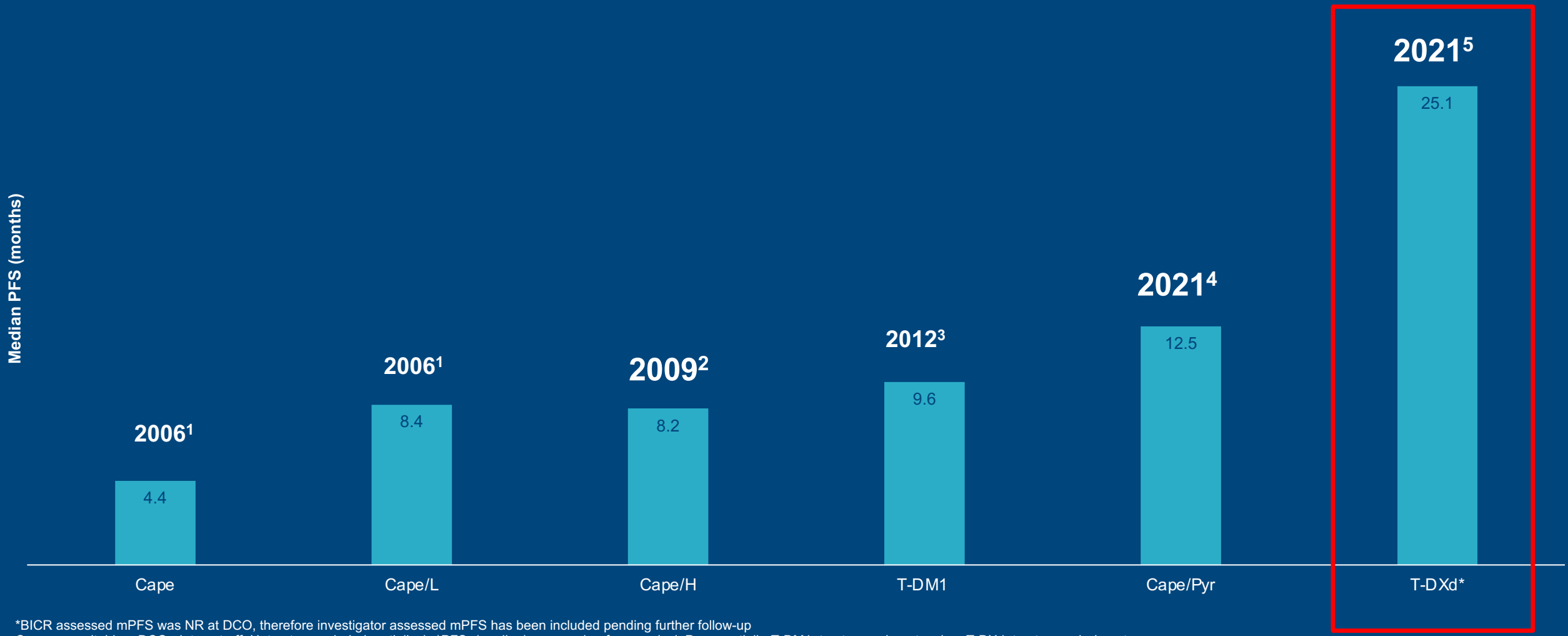
- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed and 93% of events with T-DXd were low grade (grade 1/2)

LVEF, 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 LVEF adverse events reported were asymptomatic and no cases of cardiac failure occurred

LVEF, left-ventricular ejection fraction.
[a]Patients with prior history of ILD/pneumonitis requiring steroids were excluded. [b]Left ventricular dysfunction. [c]Decreased ejection fraction.

Evolution of PFS after trastuzumab/taxane



*BICR assessed mPFS was NR at DCO, therefore investigator assessed mPFS has been included pending further follow-up

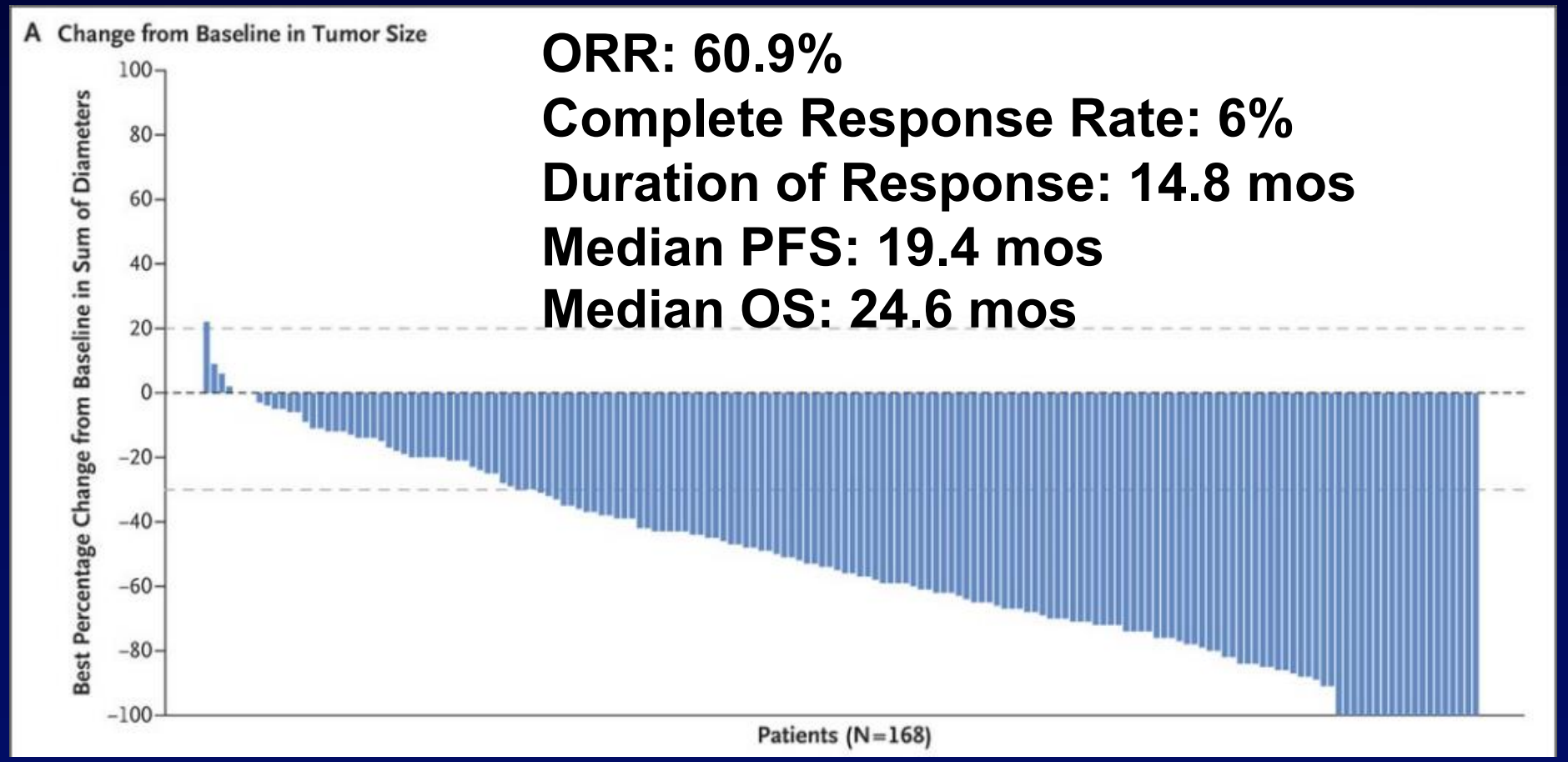
Cape=capecitabine; DCO=data cut-off; H=trastuzumab; L=lapatinib; (m)PFS=(median) progression-free survival; Pyr=pyrotinib; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan.

1. Geyer C, et al. *N Engl J Med*. 2006;355:2733–2743; 2. Von Minckwitz G, et al. *J Clin Oncol.* 2009;27:1999–2006; 3. Verma S, et al. *N Engl J Med.* 2012;367:1783–1791; 4. Xu B, et al. *Lancet Oncol.* 2021;22:351–360; 5. Cortes J, et al. Presented at ESMO. Virtual. 2021. Abstract #LBA-1.

NCCN v1.2022 Recommendations Advanced HER2+ Disease

Setting	Regimen	Evidence Level
First Line	**THP (preferred)** ***T-DXd (if recurrence <6 mos of neo/adj therapy, or <12 mos of pertuzumab)***	1
Second Line	**T-DXd (preferred)** T-DM1 (other recommended)	1 2A
Third Line and Beyond (optimal sequence unknown)		

Phase II DESTINY-Breast01: Response to DS-8201



- Dec 2019 - FDA accelerated approval for HER2+ MBC ≥2 prior lines of antiHER2-based regimens
- Feb 2020 – Added to NCCN Breast Cancer guidelines (V2.2020)

Modi S et al N Engl J Med 2020;382:610

UPDATE ON DESTINY-BREAST 01 ESMO 2021

(n = 184)

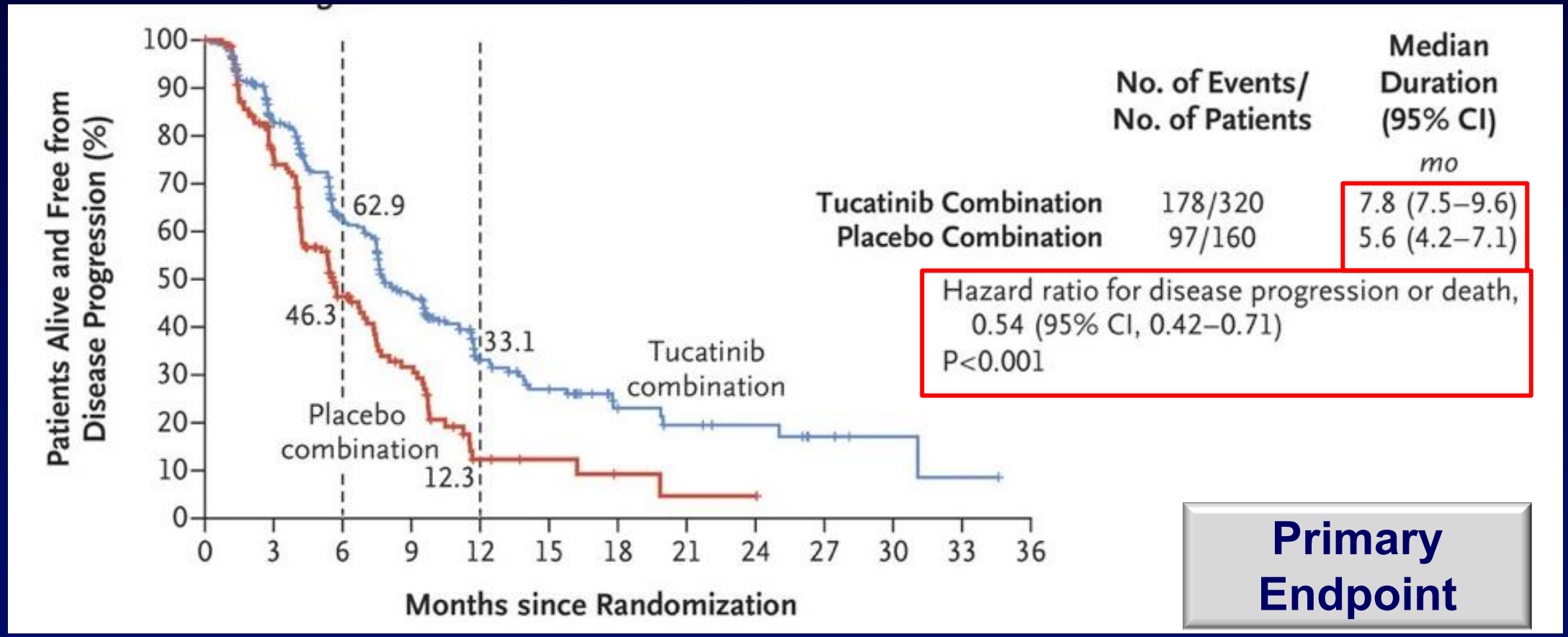
ORR	62%
Median duration of response	18.2 mo
Median PFS	19.4 mo
Median OS	29.1 mo
Pneumonitis/ILD	15.8%
Grade 5 ILD	2.7%

Saura C et al. ESMO 2021. 279P

Tucatinib

HER2CLIMB

Phase II HER2CLIMB Trial of Tucatinib + Capecitabine + Trastuzumab: PFS ITT

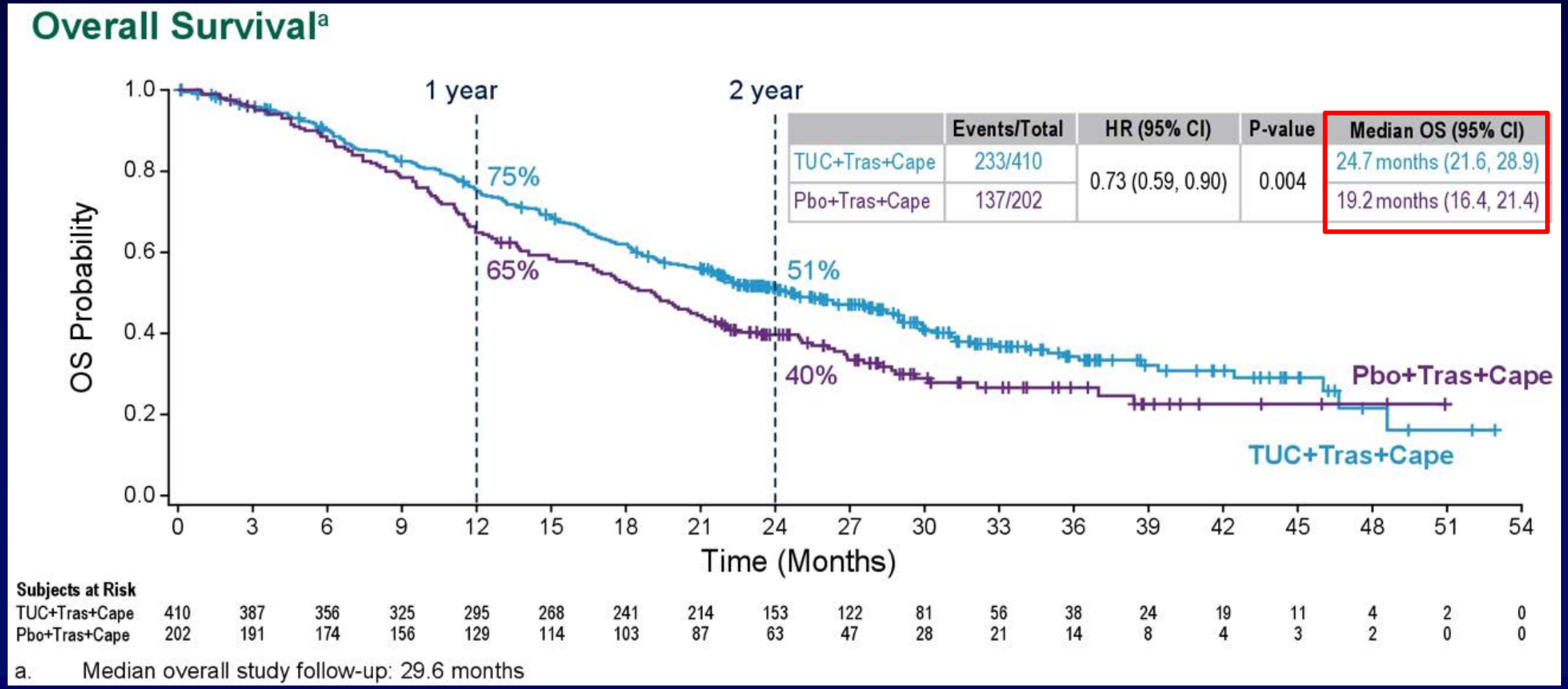


- ORR: 41% (tucatinib) vs. 23% (placebo)

Murthy RK, et al. N Engl J Med. 2020;382:597-609. Epub 2019 Dec 11.

The NEW ENGLAND JOURNAL of MEDICINE

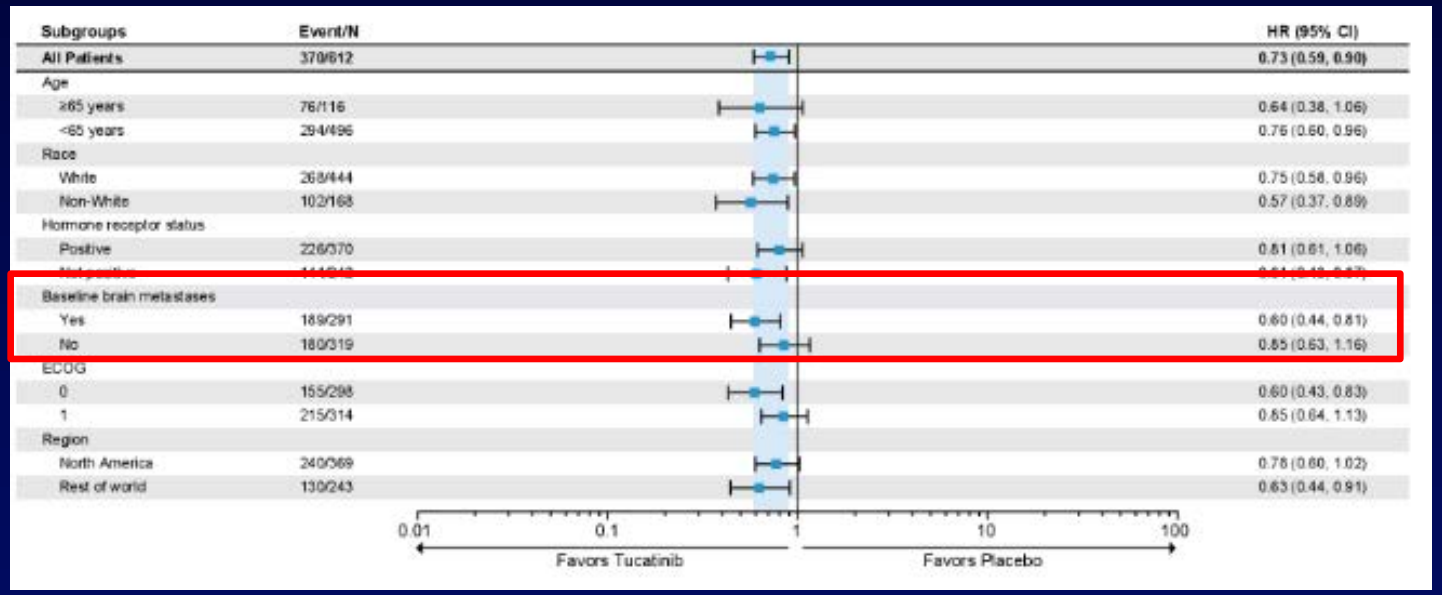
HER2CLIMB: Updated Overall Survival



	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)

Curigliano G et al. ASCO 2021. Abstract 1043.

HER2CLIMB: Subgroup Analyses



OS in Prespecified Subgroup Analyses

- OS benefit with tucatinib was generally consistent across patient subgroups

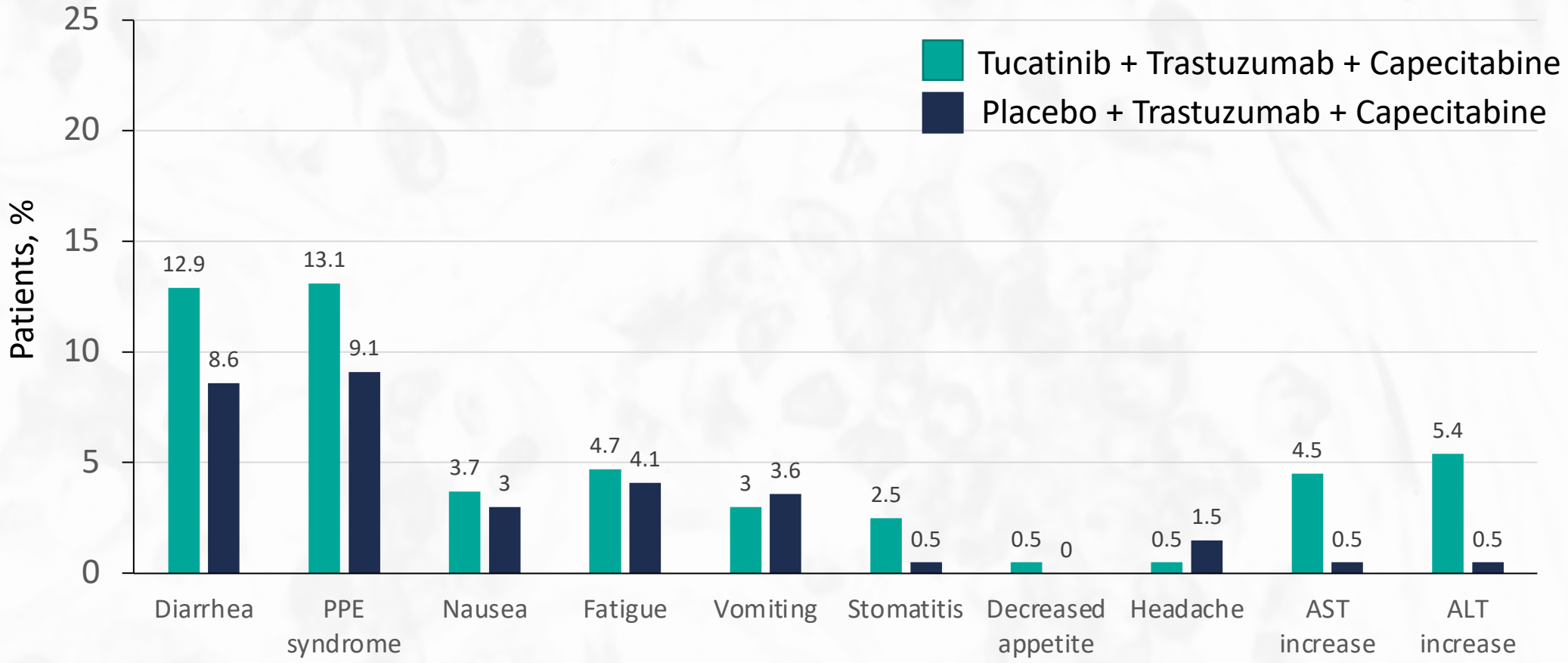
OS in an Exploratory Analysis in Patients With and Without Visceral Metastases

	Patients With Visceral Metastases (n = 455)			Patients Without Visceral Metastases (n = 157)		
	HR (95% CI)	*P*	Median OS (95% CI)	HR (95% CI)	*P*	Median OS (95% CI)
Tuc + Tras + Cape	0.70 (0.55, 0.89)	.004	21.6 mo (18.1, 25.6)	0.80 (0.48, 1.3)	.36	32.9 mo (27.7, 46.7)
PBO + Tras + Cape			16.9 mo (12.3, 19.4)			26.9 mo (20.5, NE)

- Clinically meaningful improvement of OS was observed in patients with and without visceral metastases

Curigliano G et al. ASCO 2021. Abstract 1043.

HER2CLIMB SAFETY



ALT = alanine aminotransferase; AST = aspartate aminotransferase; PPE = palmar-plantar erythrodysesthesia.

Murthy M, et al. N Engl J Med. 2020;382:597

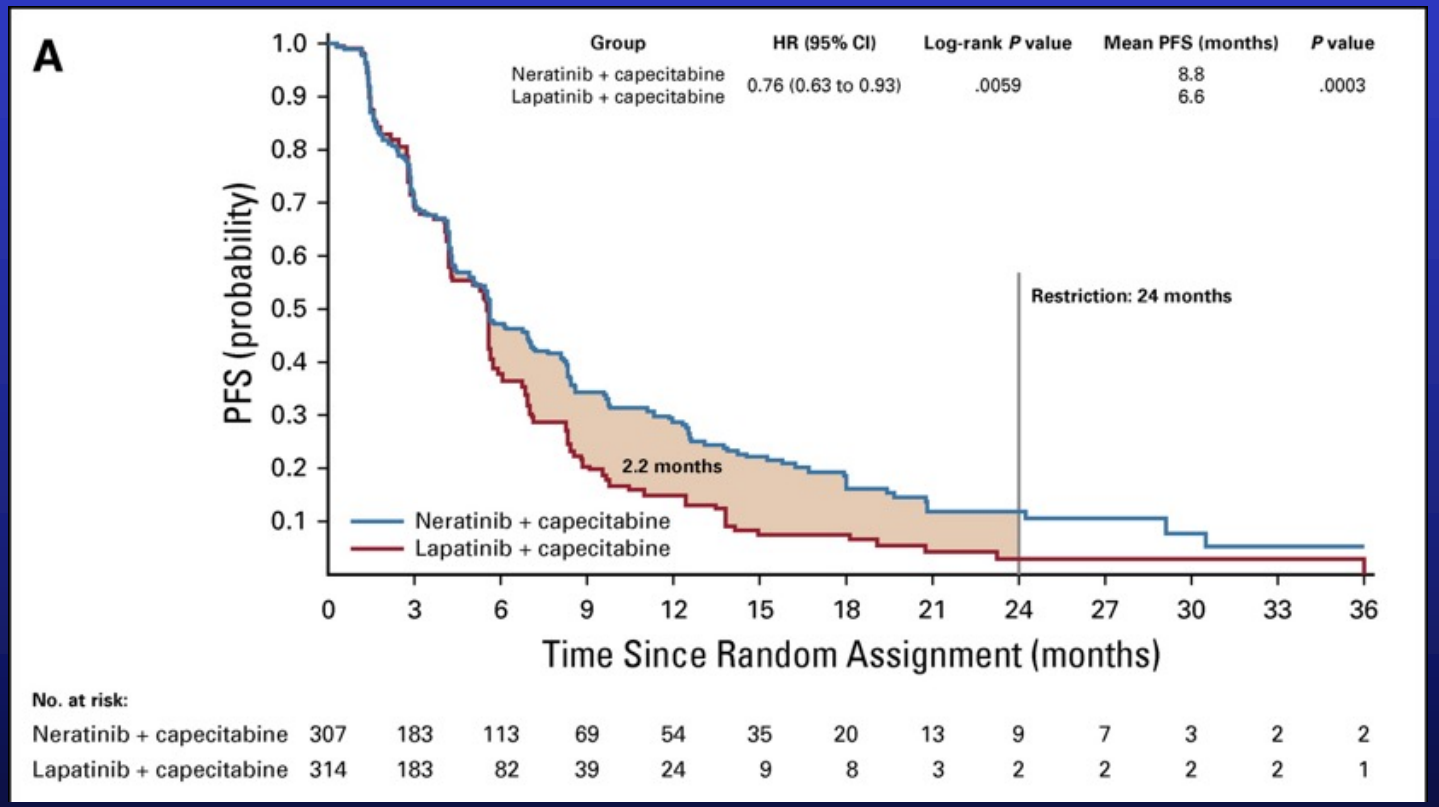
Neratinib/Capecitabine vs. Lapatinib/Capecitabine

NALA

NALA Results

Neratinib/Capecitabine vs. Lapatinib/Capecitabine

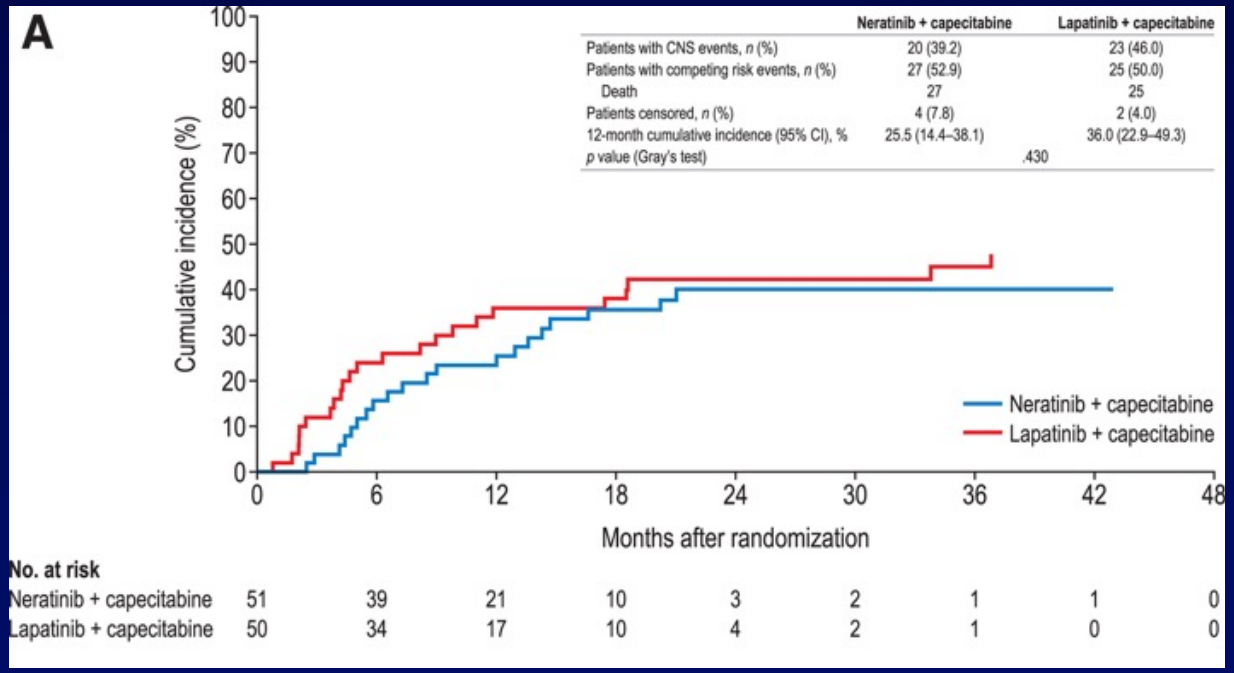
- PFS (by restricted means analysis at 24 mos)
  - 8.8 mos (neratinib) vs. 6.6 mos (lapatinib) p=0.003
- ORR: 32.8% vs 26.7% (p=NS)
- CBR: 44.5% vs 35.6% (p=0.033)
- Grade 3/4 diarrhea
  - 24% (neratinib) vs. 13% (lapatinib



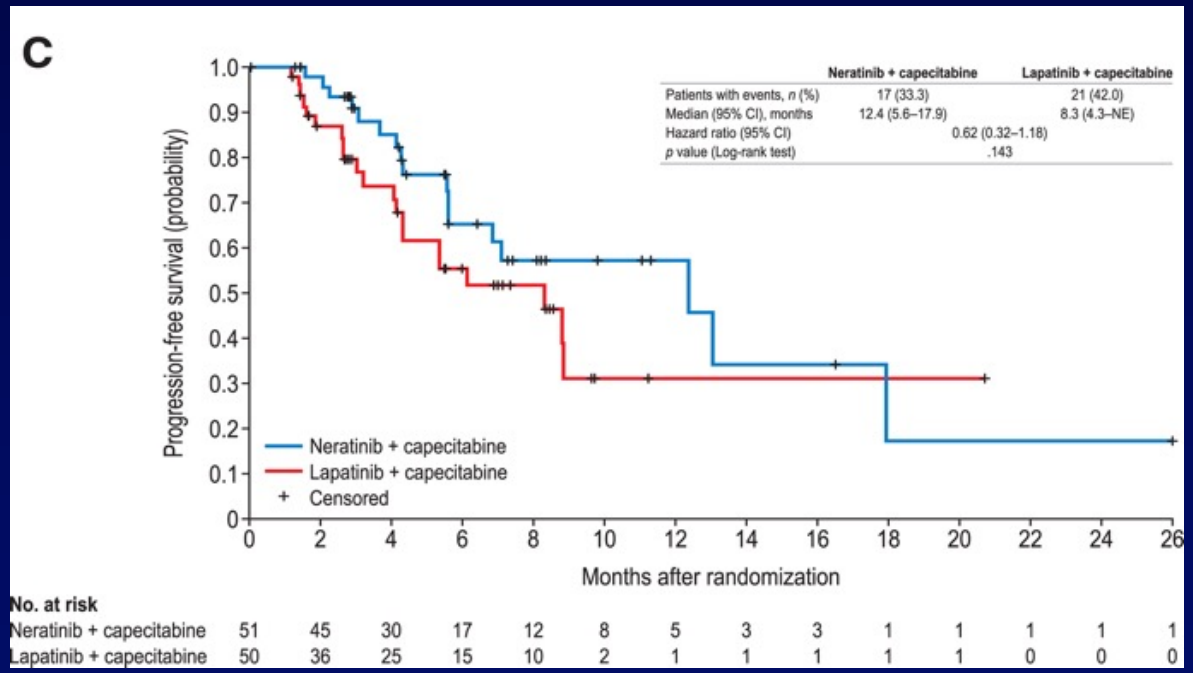
Saura C, et al. *Journal of Clinical Oncology* 2020:38(27):3138-3149.

CNS Outcomes NALA

Time to Intervention for CNS Disease



CNS PFS



Hurvitz S et al. Oncologist. 2021;26:e1327

Margetuximab

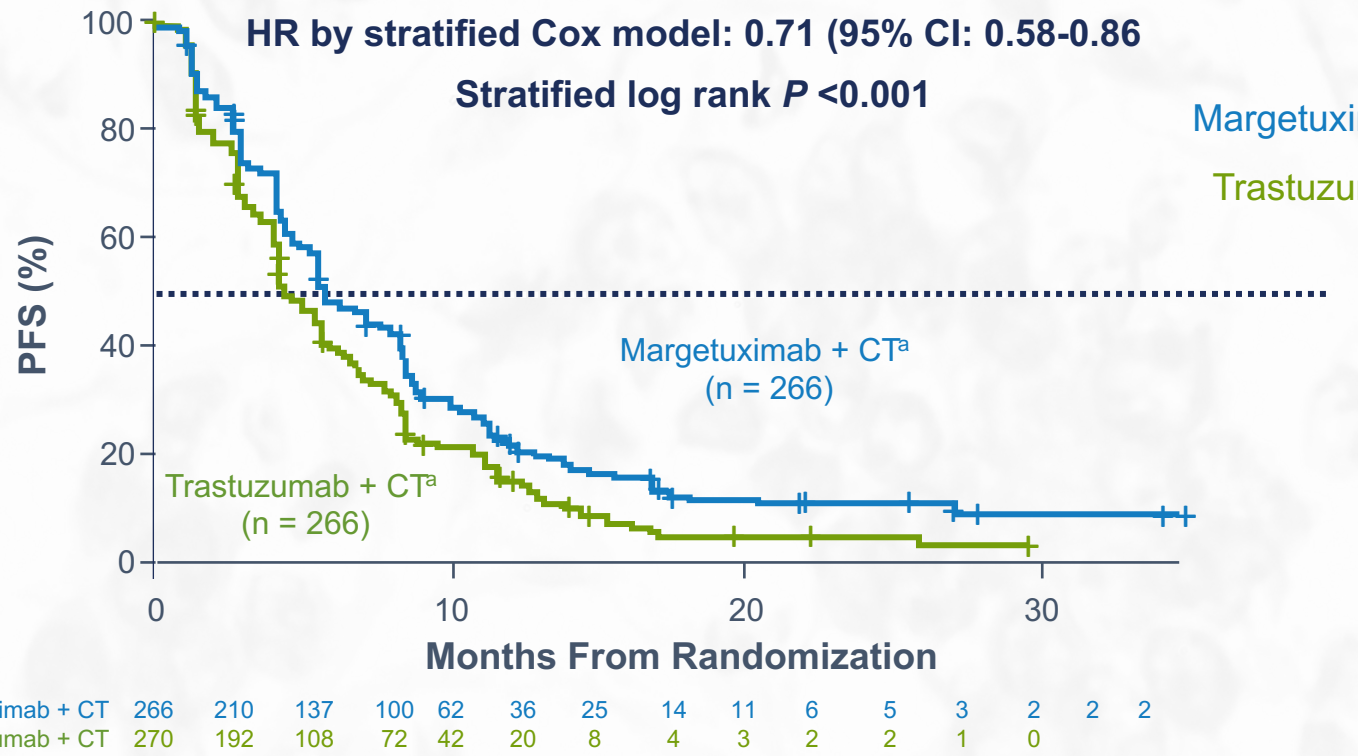
SOPHIA

SOPHIA: PFS
Margetuximab/Chemo vs. Trastuzumab/Chemo

29% reduction in risk of progression

536 patients with HER2+ advanced BC

- ≥2 prior anti-HER2 therapies, including pertuzumab
- 1-3 prior lines of tx for metastatic disease
- Treated/stable brain mets allowed



	Events, n	Median PFS, Mo (95% CI)
Margetuximab + CT*	208	5.7 (5.22-6.97)
Trastuzumab + CT*	222	4.4 (4.14-5.45)

[a]Investigator's choice of CT: capecitabine, eribulin, gemcitabine, or vinorelbine.

Rugo H, et al. JAMA Oncol 2021;7:583

SOPHIA: OS
Margetuximab/Chemo vs. Trastuzumab/Chemo

Outcome	Margetuximab + CT	Trastuzumab + CT
Events, n	131	139
Median OS (95% CI)	21.6 mo (18.86-24.05)	19.9 mo (17.54-22.28)
Stratified Cox model HR (95% CI)	0.89 (0.69-1.13) Stratified log-rank *P* = 0.33	

Genotype	Median PFS, mo (95% CI)[a]		Median OS, mo (95% CI)[a]	
	Margetuximab	Trastuzumab	Margetuximab	Trastuzumab
CD16A-158F (FF or FV) carriers (n = 437)	6.9 (5.5-8.1)	5.1 (4.1-5.6)	23.7 (18.9-28.3)	19.5 (16.8-22.3)
HR (95% CI)	0.68 (0.52-0.90) *P* = 0.005		0.79 (0.61-1.04) *P* = 0.087	
CD16A-158VV homozygotes (n = 69)	4.8 (2.5-5.6)	5.6 (2.9-11.0)	19.7 (15.7-23.9)	33.3 (16.7-33.3)
HR (95% CI)	1.78 (0.87-3.62) *P* = 0.110		1.65 (0.82-3.32) *P* = 0.157	
CD16A-158FF homozygotes (n = 192)	8.2 (5.5-10.5)	5.6 (4.5-8.3)	23.3 (18.6-32.8)	18.4 (14.6-22.3)
HR (95% CI)	0.69 (0.46-1.05) *P* = 0.080		0.69 (0.47-1.02) *P* = 0.062	
CD16A-158FV heterozygotes (n = 245)	6.3 (5.5-7.2)	4.3 (4.0-5.6)	25.5 (18.3-NE)	20.0 (17.2-22.3)
HR (95% CI)	0.71 (0.50-1.01) *P* = 0.055		0.88 (0.61-1.27) *P* = 0.498	

CD16A-158F carriers (lower-affinity phenylalanine genotypes FF or FV) made up 86% (437/506) patients with available genotype.

Rugo H, et al. JAMA Oncol 2021;7:583

Final Overall Survival Results from the SOPHIA Study for Patients with HER2-Positive Metastatic Breast Cancer Did Not Demonstrate a Statistically Significant Advantage with Margetuximab Over Trastuzumab

Press Release – September 07, 2021

"Final overall survival (OS) results of the SOPHIA Phase 3 study in adult patients with metastatic HER2-positive breast cancer did not demonstrate a statistically significant advantage for margetuximab over trastuzumab.

The final OS analysis of the SOPHIA study was performed after 385 OS events occurred in the intent-to-treat (ITT) population. As per the study protocol, OS was defined as the number of days from randomization to the date of death (from any cause). The final OS analysis for the ITT population did not demonstrate a statistically significant advantage for margetuximab plus chemotherapy compared to that of patients who received trastuzumab plus chemotherapy (hazard ratio [HR] = 0.95; 95% Confidence Interval [CI]: 0.77-1.17; P = 0.62). In this overall ITT population, the median survival was 21.6 months in patients treated with margetuximab plus chemotherapy (N = 266) compared to 21.9 months in patients treated with trastuzumab plus chemotherapy (N = 270).

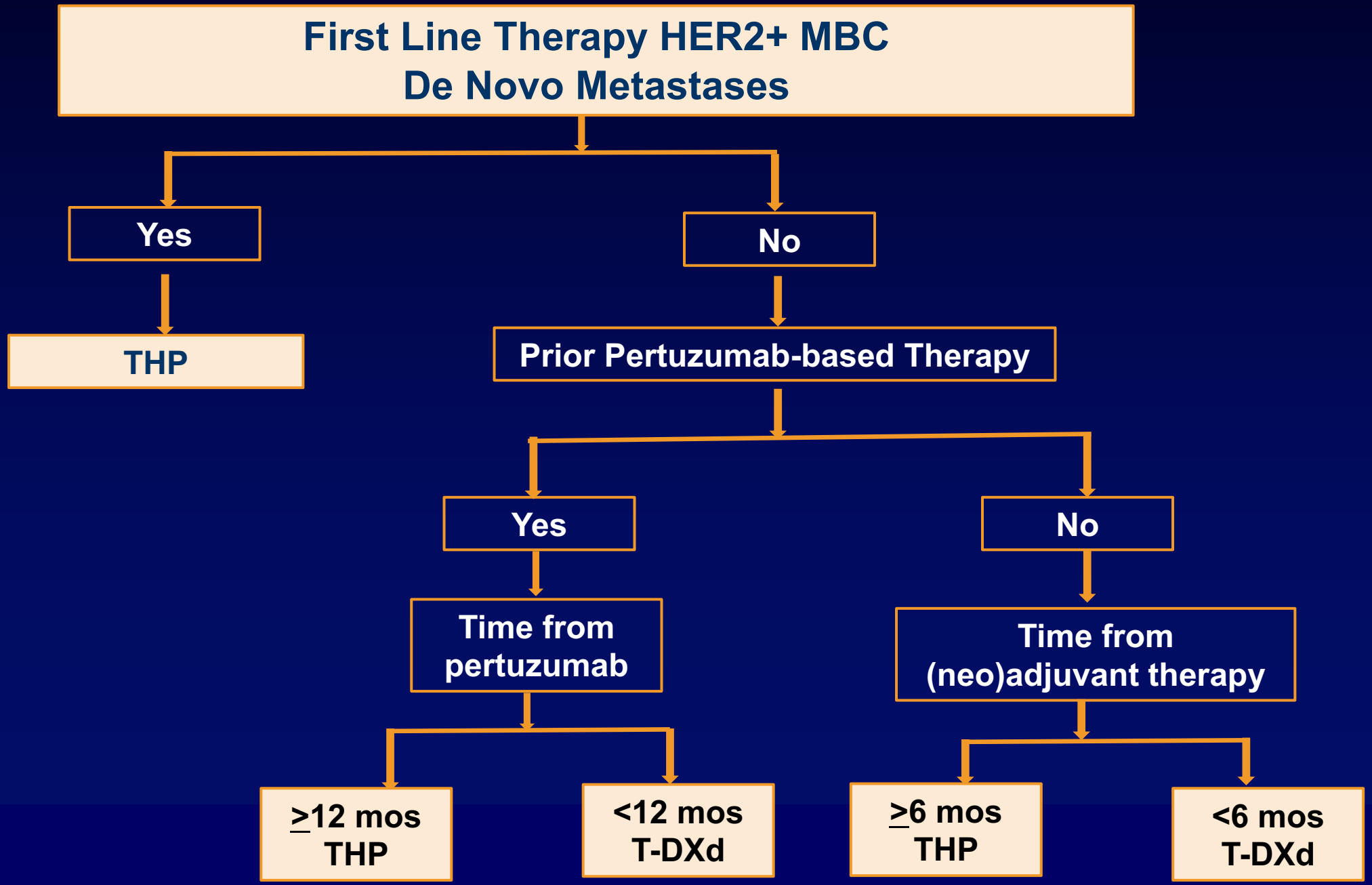
The safety profile at the time of the final OS analysis of SOPHIA was similar to what was previously reported."

https://www.globenewswire.com/news-release/2021/09/07/2292944/0/en/MacroGenics-Announces-Final-Overall-Survival-Results-from-SOPHIA-Study-of-MARGENZA-in-Patients-with-HER2-Positive-Metastatic-Breast-Cancer.html

PFS 3rd line setting and beyond

	Drugs	ORR (%)	Med PFS (mos)	Med OS (mos)
EGF104900 Blackwell K et al. J Clin. Oncol 2010 Blackwell K et al. J. Clin Oncol 2012	Lapatinib	7	2	9.5
	Lapatinib/Trastuzumab	10	3	14
TH3RESA Krop I et al, Lancet Oncol 2014 Krop I et al, Lancet Oncol 2017	Treatment Physician's Choice	NR	3.3	15.8
	T-DM1	NR	6.2	22.7
NALA Saura C et al. J Clin Oncol 2020	Lapatinib/Capecitabine	27	5.5	22.2
	Neratinib/Capecitabine	33	5.6	24.0
SOPHIA Rugo H et al. JAMA Oncol 2021	Trastuzumab/chemo	14	4.9	19.8
	Margetuximab/chemo	25	5.8	21.6
HER2CLIMB Murthy et al. N Engl J Med 2020 Curigliano et al ASCO 2021	Trastuzumab/Capecitabine	23	4.9	19.2
	Tucatinib/Trastuzumab/Capecitabine	**41**	**7.6**	**24.7**
DESTINY-BREAST-01 Saura C et al. ESMO 2021	T-DXd	**62**	**19.4**	**29**

Summary Recommendations


First Line Therapy HER2+ MBC
De Novo Metastases
Yes
No
THP
Prior Pertuzumab-based Therapy
Yes
No
Time from pertuzumab
Time from (neo)adjuvant therapy
≥12 mos THP
<12 mos T-DXd
≥6 mos THP
<6 mos T-DXd

NCCN v1.2022 Recommendations Advanced HER2+ Disease

Setting	Regimen	Evidence Level
First Line	**THP (preferred)** *T-DXd (if recurrence <6 mos of neo/adj therapy, or <12 mos of pertuzumab)*	1
Second Line	**T-DXd (preferred)** T-DM1 (other recommended) Tucatinib/capecitabine/trastuzumab (if CNS metastases)	1 2A
Third Line and Beyond (optimal sequence unknown)	**Tucatinib/Capecitabine/Trastuzumab (preferred in those with systemic & CNS mets)**	1
	T-DXd (*if not used 2nd line)	2A
	T-DM1 (*no data regarding benefits after T-DXd)	
	Trastuzumab + docetaxel or vinorelbine or paclitaxel (+/- carbo)	2A
	Capecitabine + trast or lapatinib	2A
	Trastuzumab + lapatinib	2A
	Neratinib + capecitabine	2A
	Margetuximab + chemo	2A