

Algoritmo do tratamento do câncer de mama metastático HER2+ em 2023

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Disclosures

Clinical study: Astra Zeneca, Gilead, MSD, Roche, Sanofi

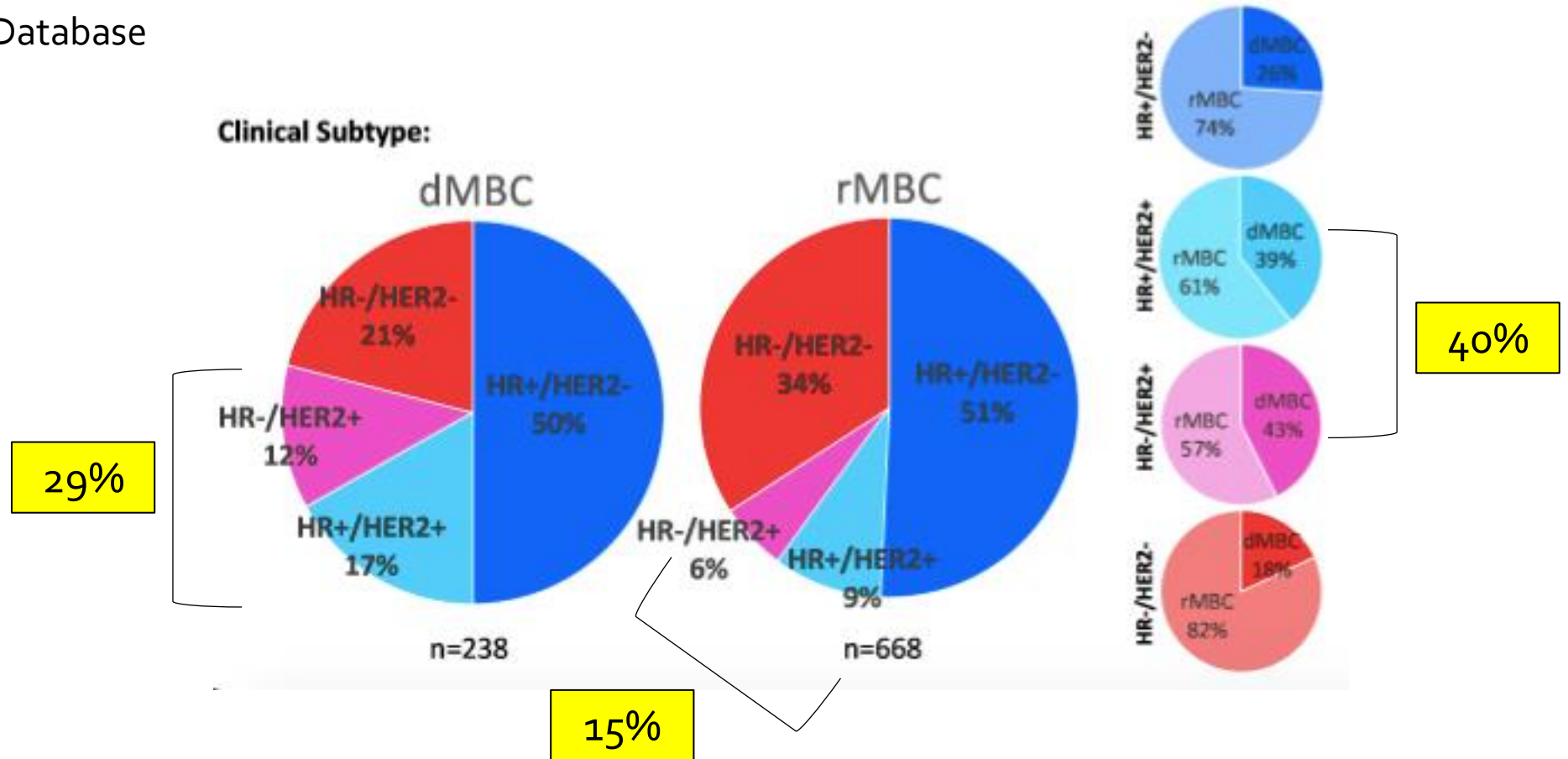
Consultant: Astra Zeneca, Daiichi Sankyo, Genomic Health, Gilead, Libbs, Lilly, MSD, Novartis, Pfizer, Roche, Zodiac

Travel expenses: AstraZeneca, Daiichi Sankyo, Roche

Personal opinion may not reflect the Instituto Nacional de Câncer orientation

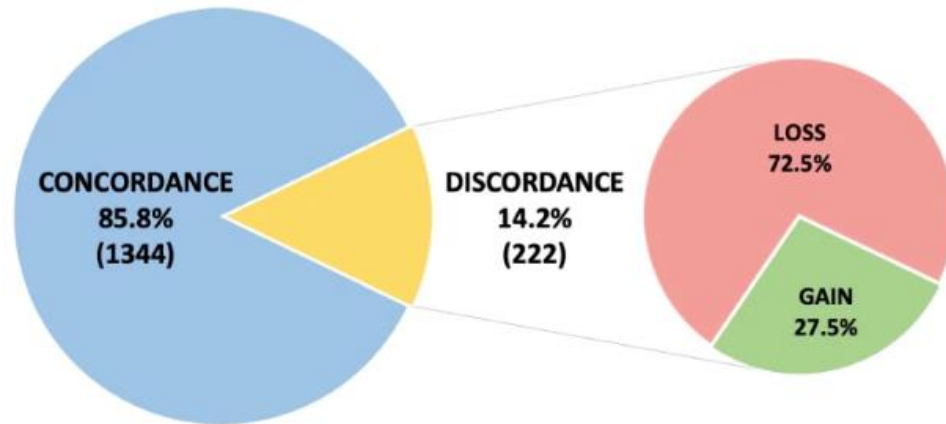
The contribution of clinical subtype among patients with dnMBC and rMBC

2001- 2017
University of North Carolina
Prospective MBC Database

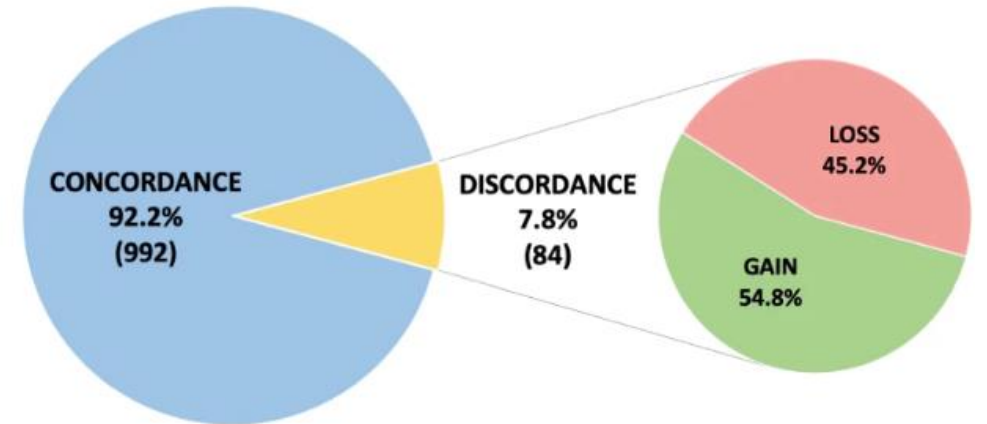


Phenotypic discordance between primary and metastatic breast cancer

a. Global hormone receptor (HR) status on primary tumour and metastases



b. HER2 status on primary tumour and metastases



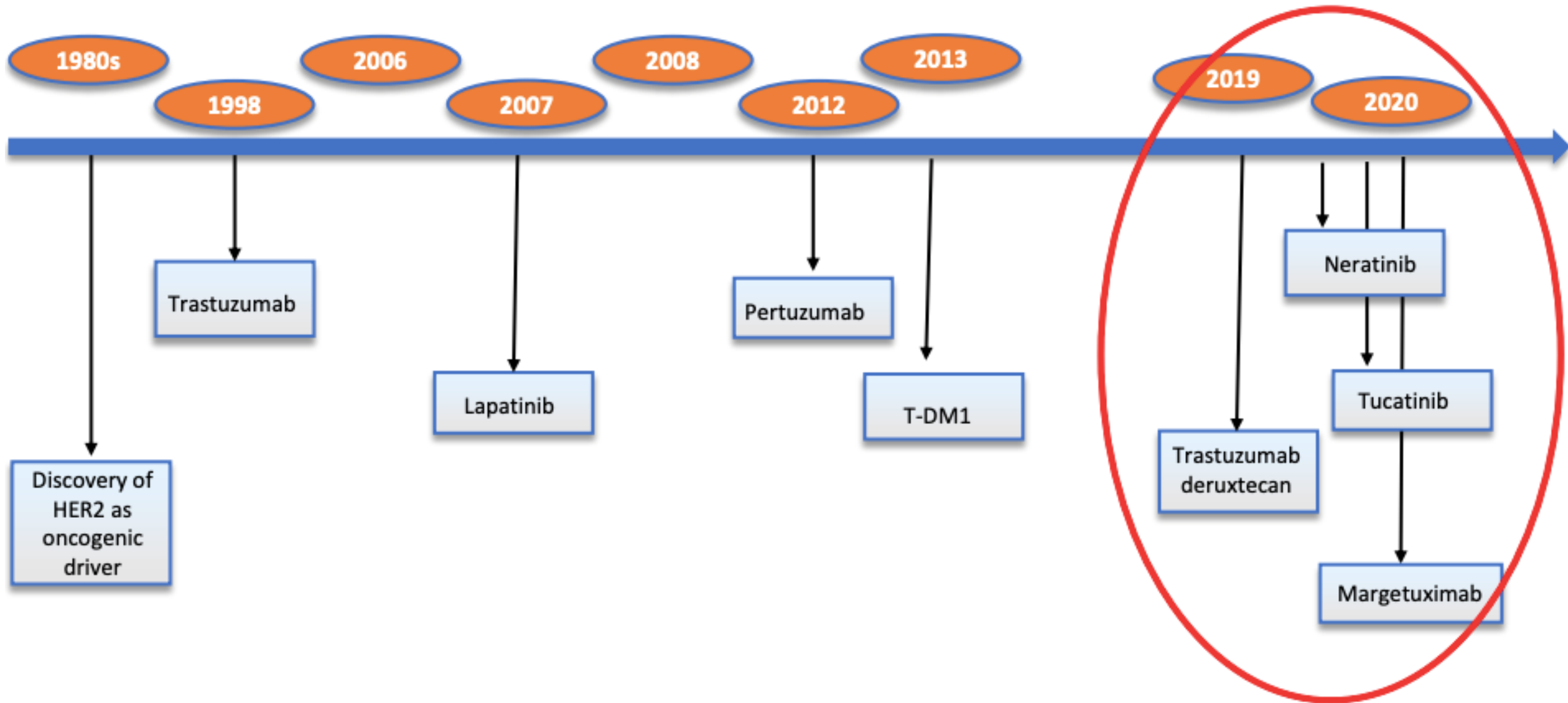
Real-life multicenter French ESME cohort n= 1677

The discordance rate appeared similar across different biopsy sites

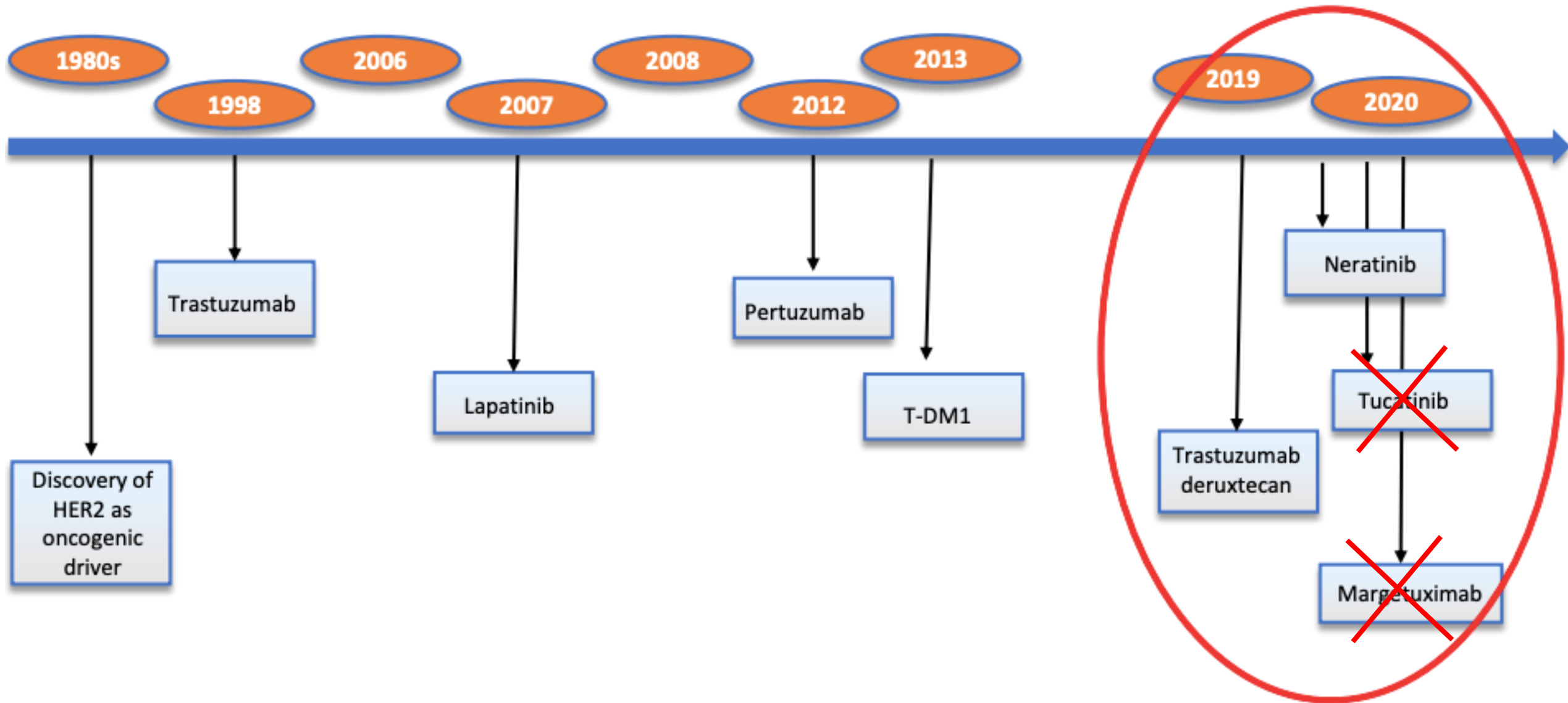
Real-world-data on overall survival (OS) in metastatic breast cancer

OS (m)	Year of Diagnosis					
	2008	2009	2010	2011	2012	2013
HR+ HER2- (N=9.908)	43.7 (40.2-46.6)	42.0 (38.9-44.6)	40.9 (38.0-43.4)	42.0 (39.2-45.0)	44.5 (41.8-47.3)	40.3 (37.8-ND)
HER2+ (N=2.861)	38.6 (33.6-44.6)	42.3 (38.3-50.8)	40.1 (35.2-45.6)	42.3 (36.5-49.8)	51.1 (46.5-NR)	Not Reached
HR- HER2- (N=2.317)	15.1 (12.7-16.4)	15.1 (13.0-17.4)	14.7 (13.2-17.0)	14.0 (11.4-15.9)	13.9 (11.4-15.9)	14.1 (12.5-15.5)

HER2-Targeted Therapies for MBC: Timeline of Approvals



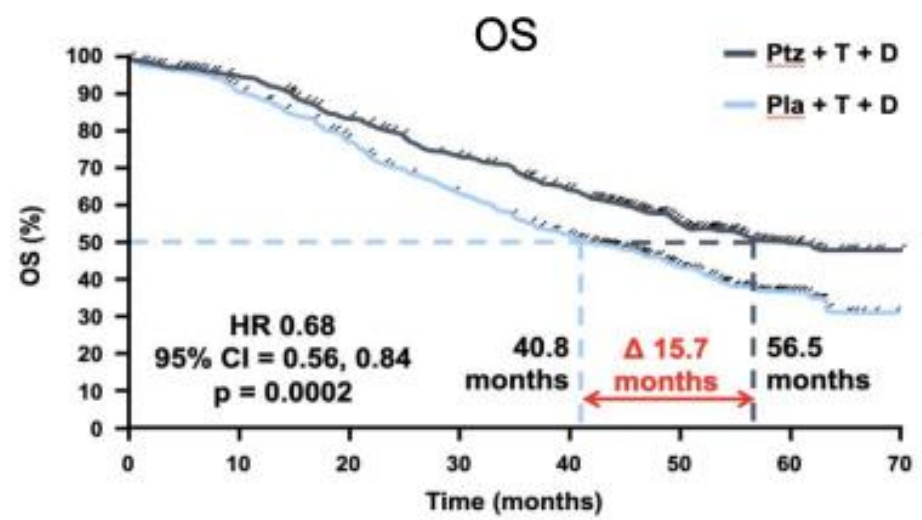
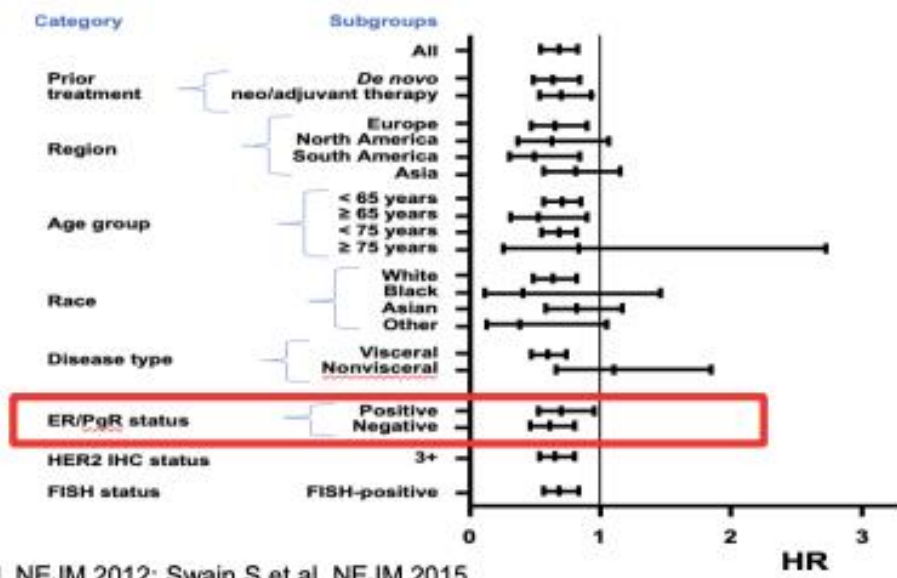
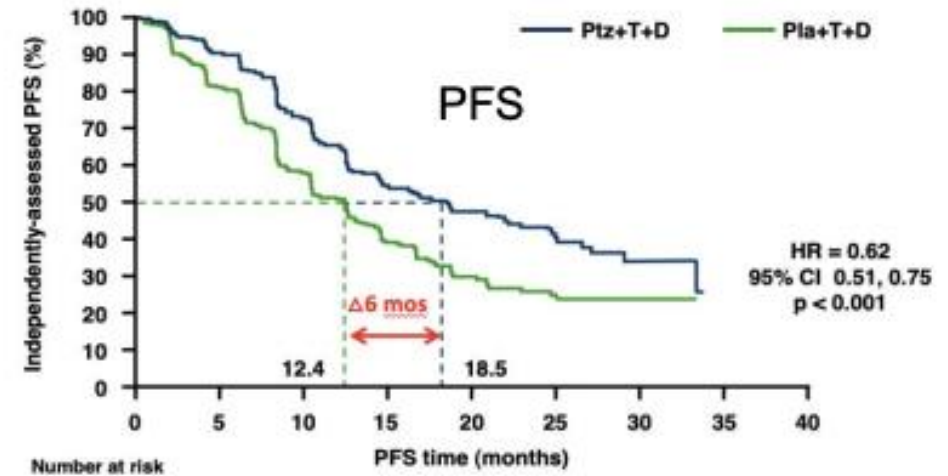
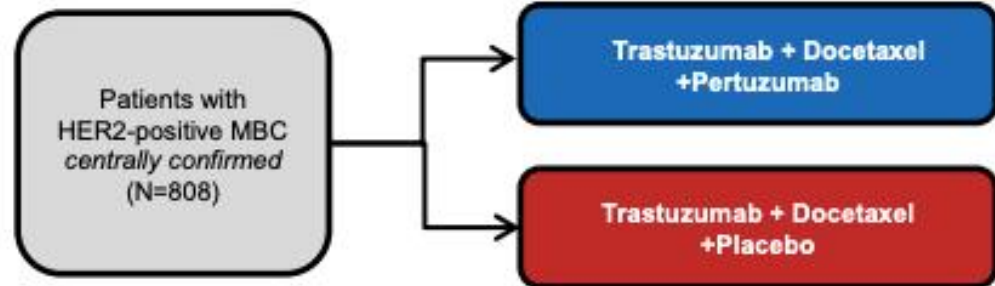
HER2-Targeted Therapies for MBC: Timeline of Approvals



1st Line

CLEOPATRA Trial :

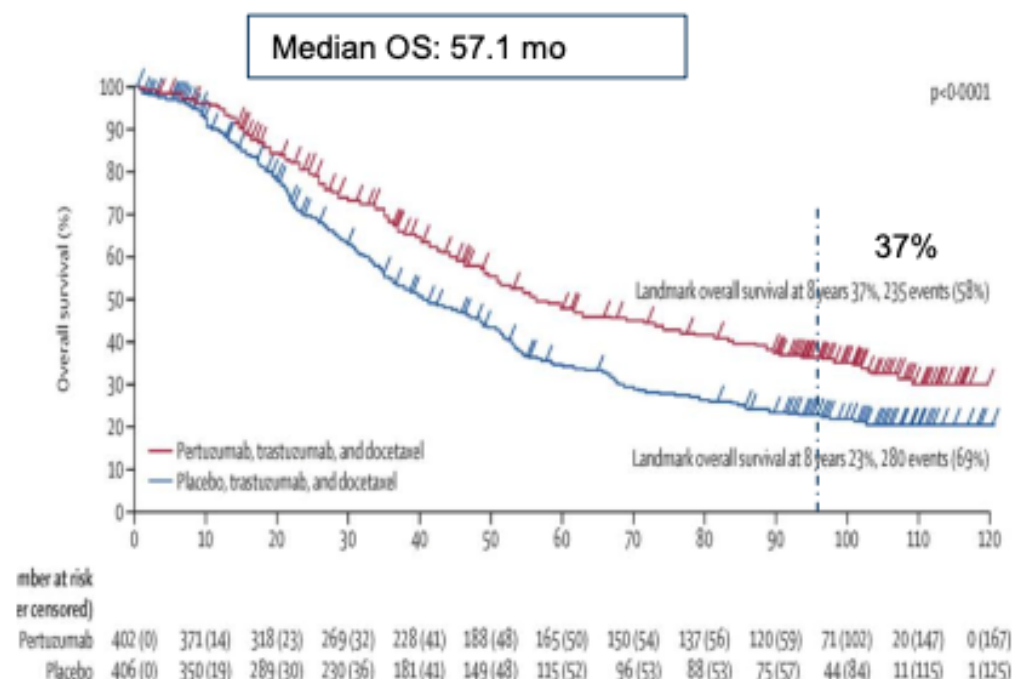
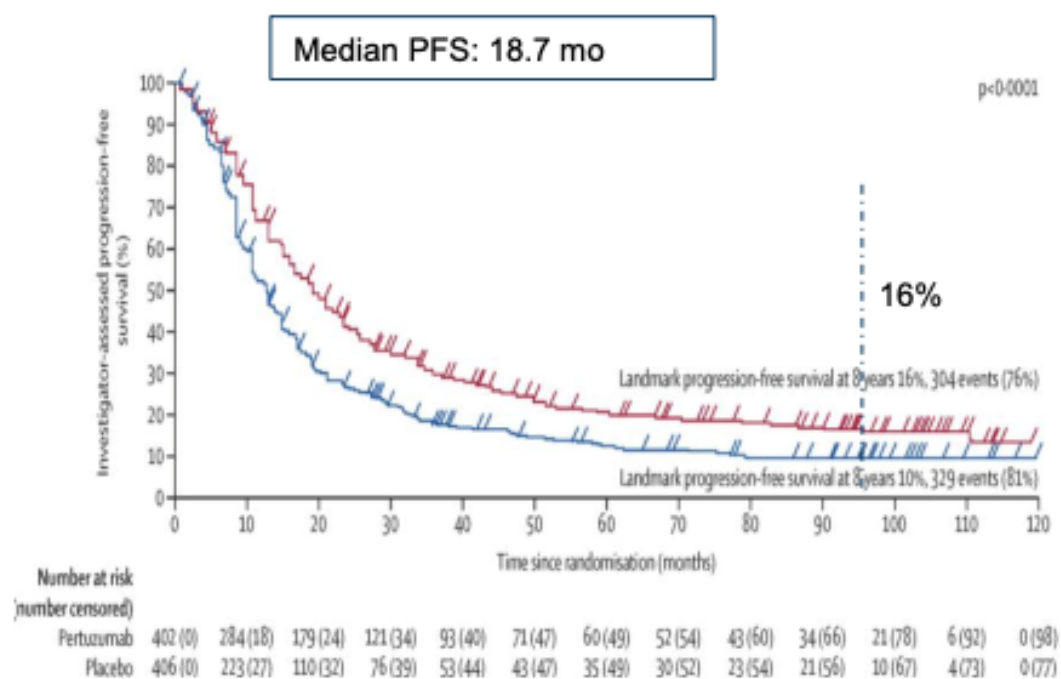
Adding Pertuzumab to Docetaxel +Trastuzumab Improves PFS & OS



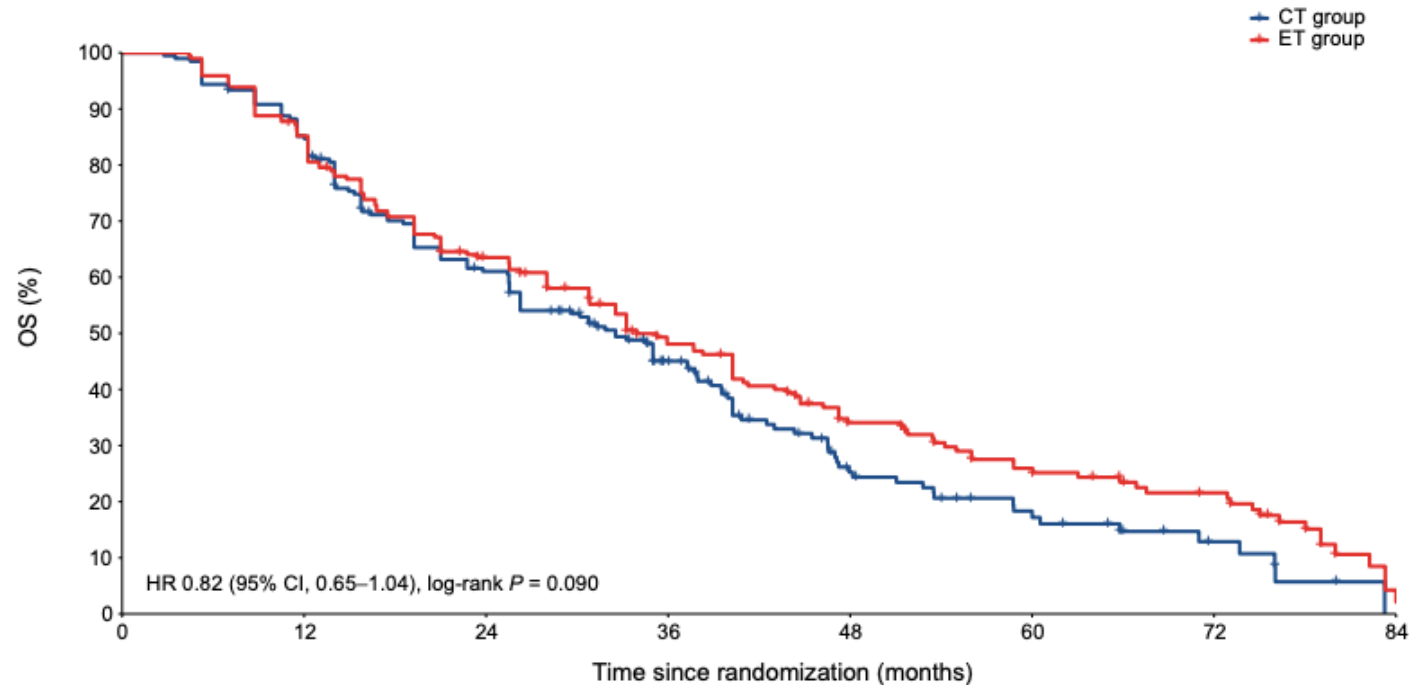
CLEOPATRA End-of-Study Results:

Adding Pertuzumab to Docetaxel +Trastuzumab Improves PFS & OS

(median follow-up ~100 months)



Trastuzumab Plus Endocrine Therapy or Chemotherapy as First-line Treatment for Patients with Hormone Receptor–Positive and HER2-Positive Metastatic Breast Cancer (SYSUCC-002)

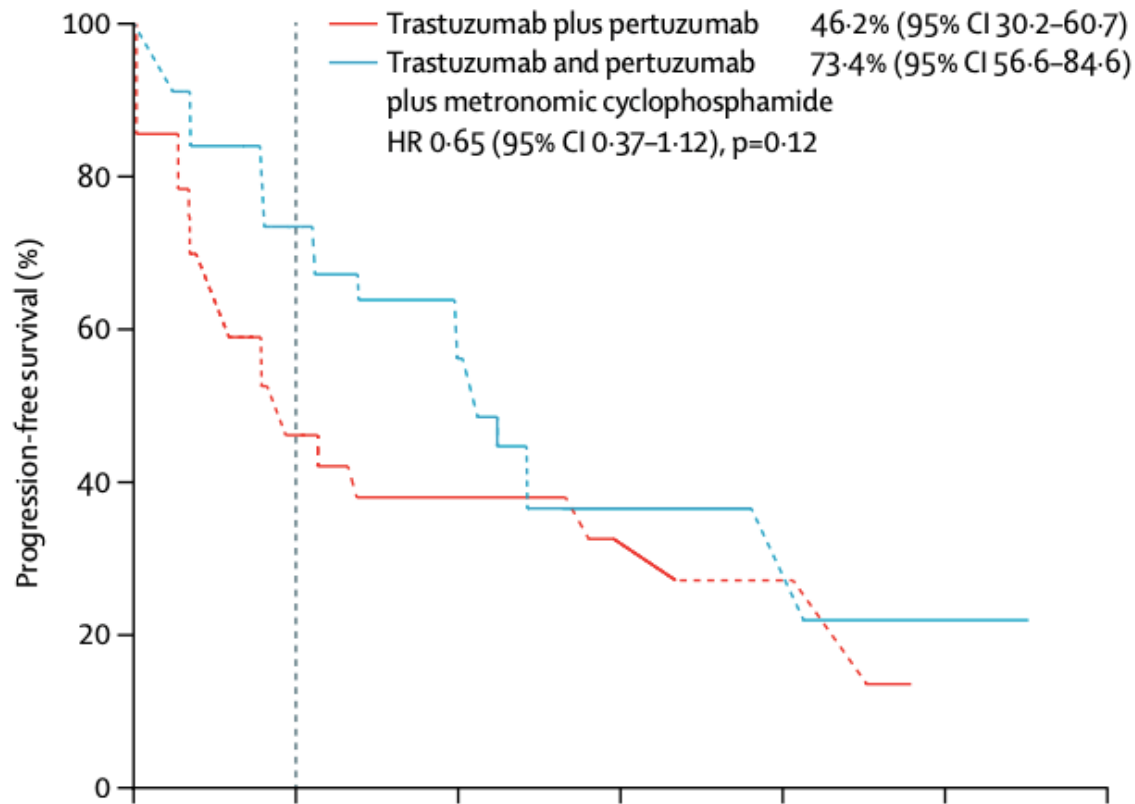


Trastuzumab plus endocrine therapy was noninferior to trastuzumab plus chemotherapy in patients with HR+HER2+ MBC

Number at risk
(number censored)

	0	12	24	36	48	60	72	84
CT group	196 (0)	166 (1)	114 (7)	66 (27)	28 (40)	16 (45)	6 (51)	0 (51)
ET group	196 (0)	166 (1)	118 (7)	78 (20)	49 (27)	33 (32)	22 (38)	2 (46)

EORTC 75111-10114: an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group



80 patients, 70% frail

Addition of metronomic oral cyclophosphamide increased median progression-free survival by **7 months** compared with dual HER2 blockade alone

2nd Line

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

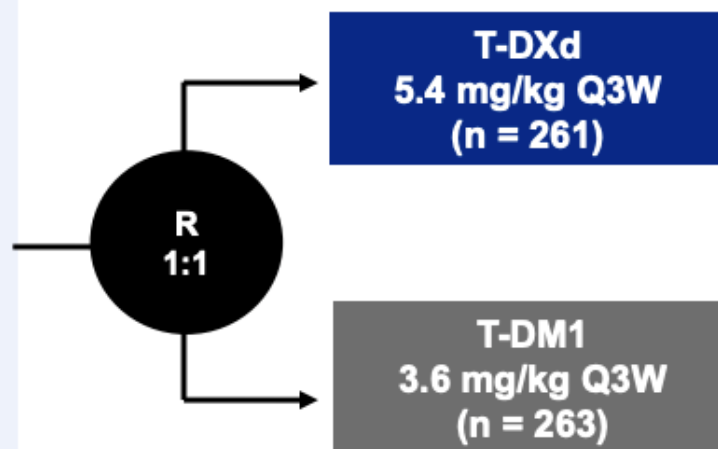
An open-label, multicenter study (NCT03529110)

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

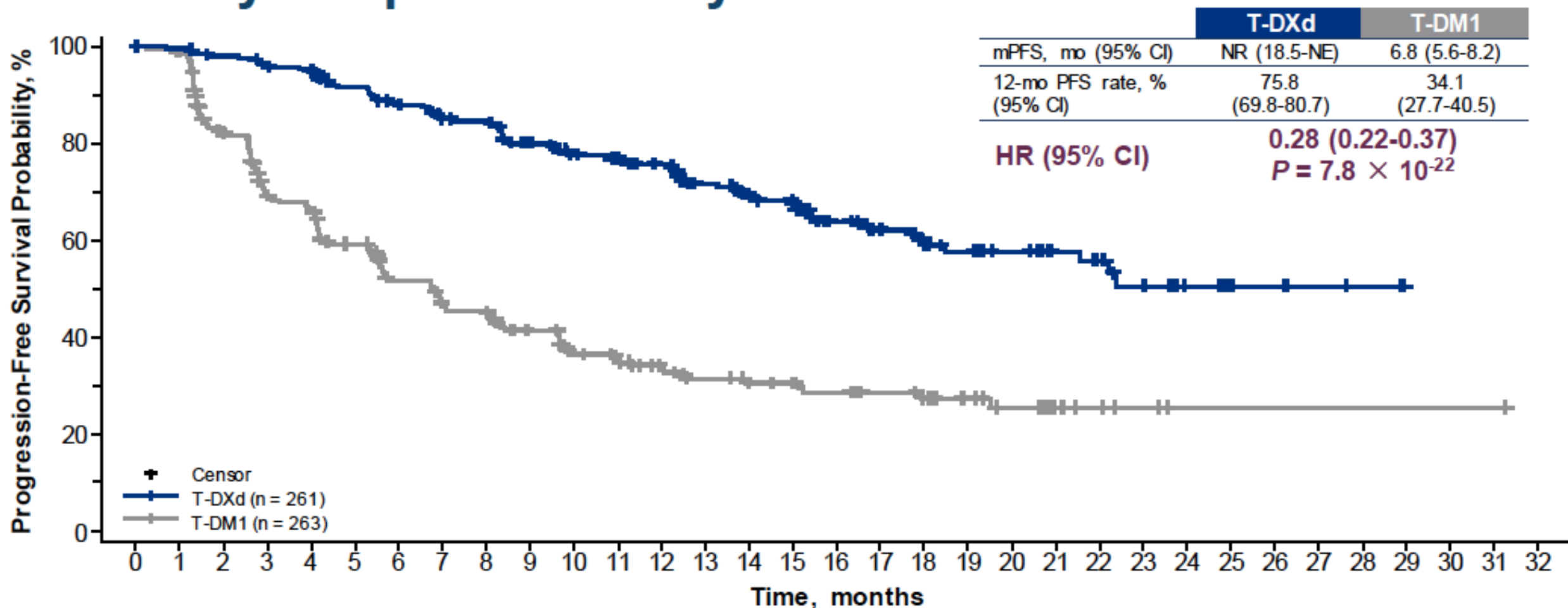
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Prior therapy for MBC:

- 100% received prior trastuzumab
- 60% received prior pertuzumab
- 16% received HER2 TKI
- 50% received 1 line of therapy for MBC



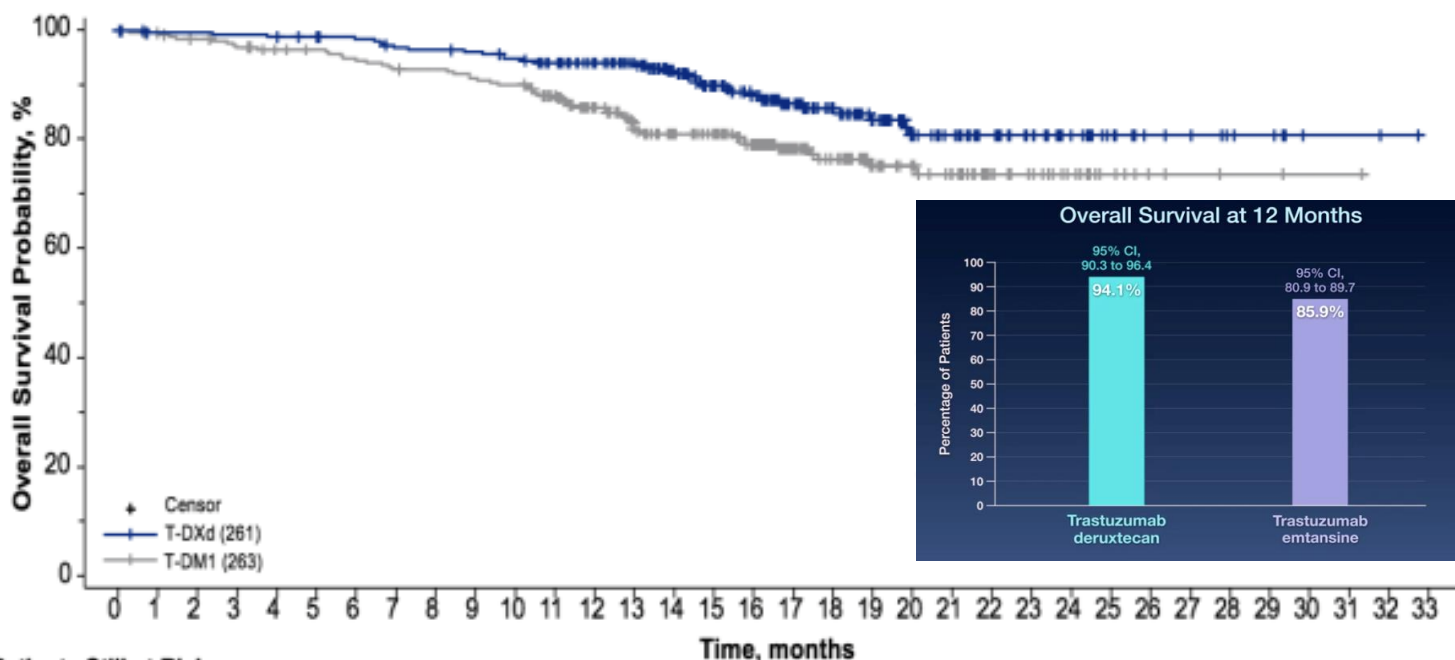
Primary Endpoint: PFS by BICR



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	0

DB03 Secondary Endpoints: Overall Survival and Response Rate



Patients Still at Risk:

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
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)
^aP = .007172, but does not cross pre-specified boundary of P < .000265

	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]
	<i>P</i> < .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)

CLEOPATRA, ORR= 80% CR= 5.5%

HER2CLIMB: RANDOMIZED PHASE II TRIAL

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
 - Previously treated stable brain metastases
- **Untreated brain metastases not needing immediate local therapy**
- **Previously treated progressing brain metastases not needing immediate local therapy**
- No evidence of brain metastases

N = 410

R*
2:1

N = 202

Tucatinib + trastuzumab + capecitabine (21-day cycle)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1,000 mg/m² PO BID (days 1-14)

Placebo + trastuzumab + capecitabine (21-day cycle)

Placebo
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)
+
Capecitabine 1,000 mg/m² PO BID (days 1-14)

48% CNS metastases

36% *de novo* metastatic breast cancer

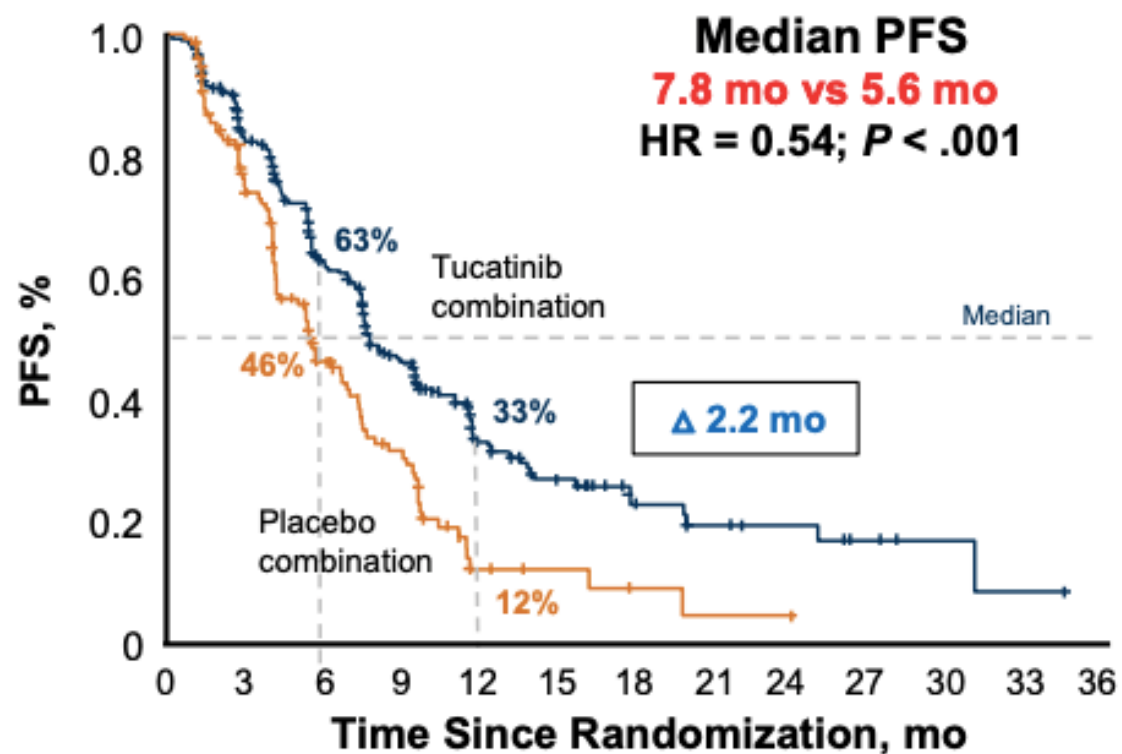
Median number of lines in the metastatic setting: 3(1-14)

Primary endpoint: PFS

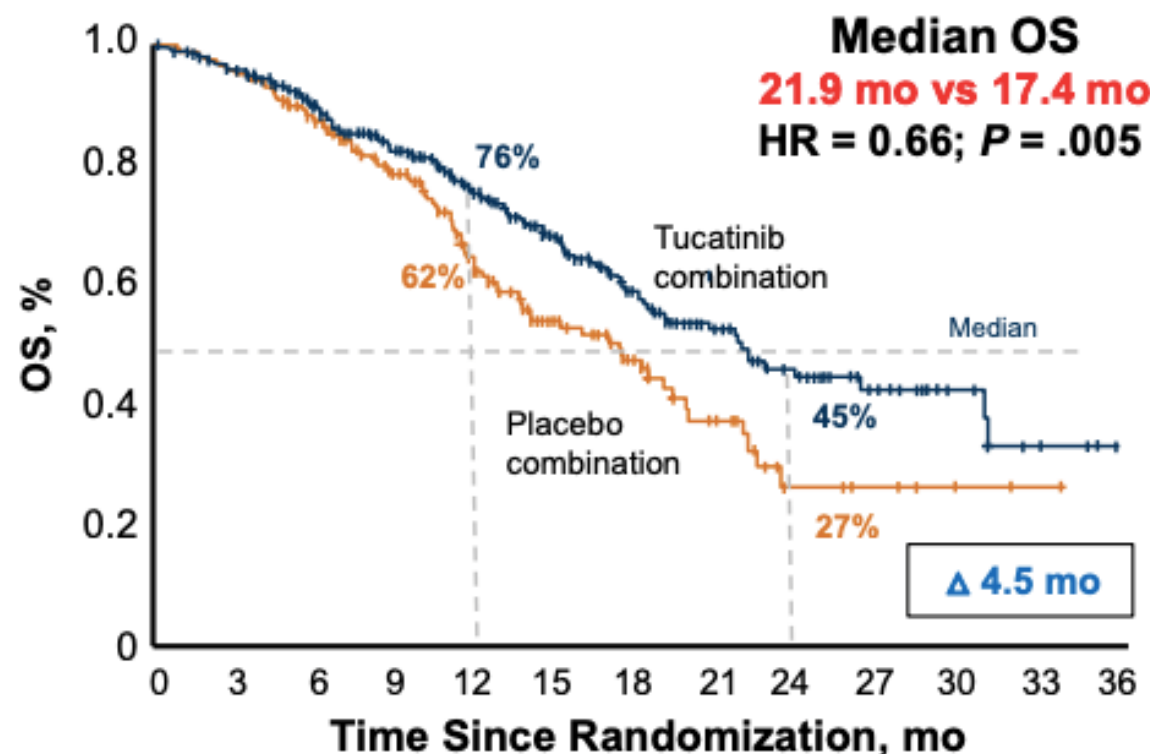
HER2CLIMB: Randomized Phase 2 Trial of Tucatinib

Median duration of followup of 14mo

Tucatinib Improves PFS and OS



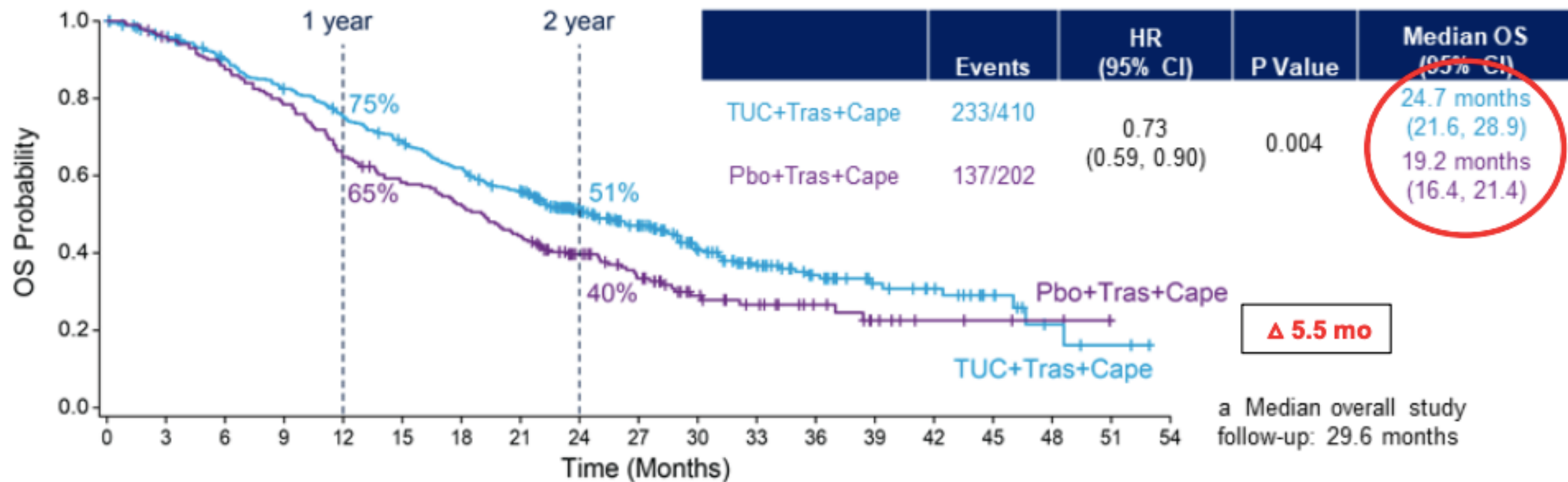
No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Tuc + tras + cape	320	235	152	96	40	29	15	10	8	4	2	1	0
Pbo + tras + cape	160	94	45	27	6	4	2	1	1	0	0	0	0



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Tuc + tras + cape	410	388	322	245	178	123	80	51	34	20	10	4	0
Pbo + tras + cape	202	191	160	119	77	48	32	19	7	5	2	1	0

HER2CLIMB: Updated Overall Survival

Median follow-up 29.6 months

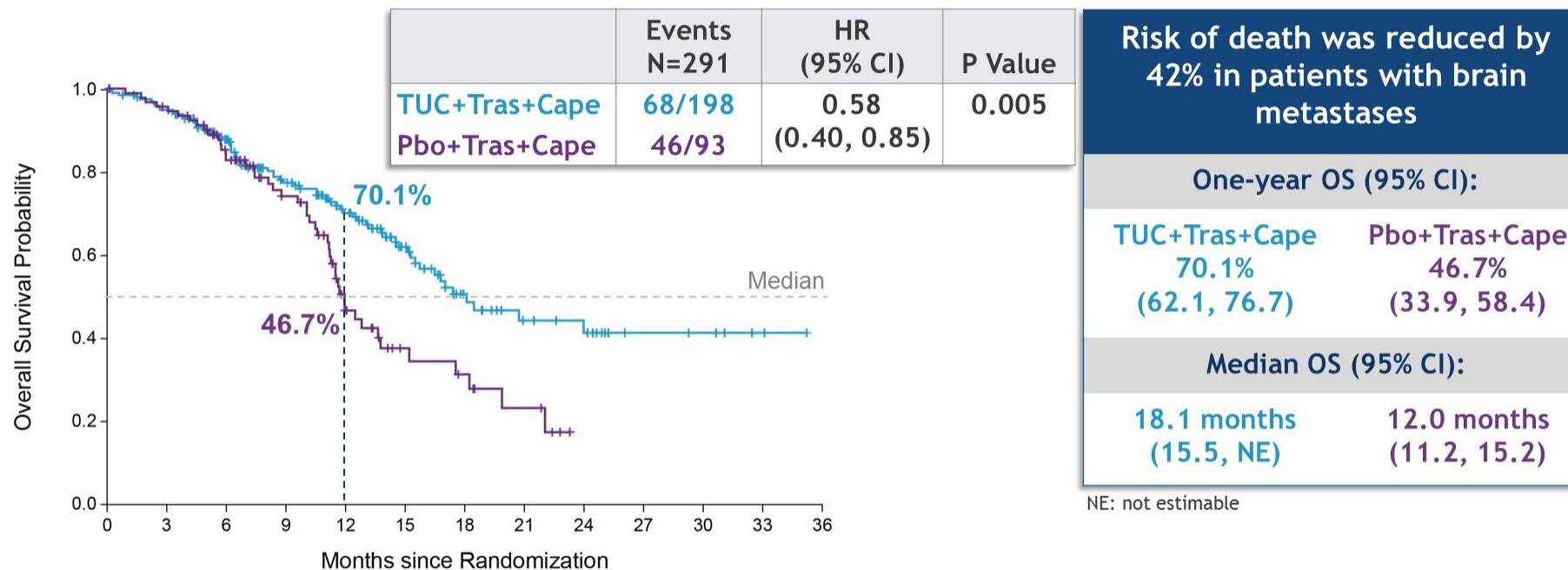


Subjects at Risk

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

- 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.

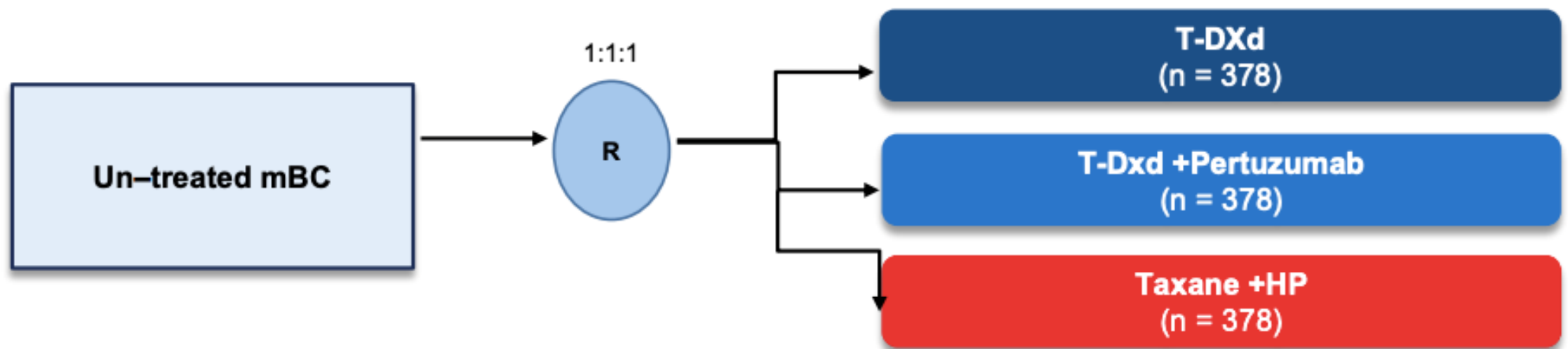
OS Benefit in Patients with Brain Metastases



HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

What is in the horizon?

DESTINY Breast-09 Trial : 1st Line HER2+ MBC



Primary endpoint: PFS

What is in the horizon?

Anti-HER2 combinations

CDK4/6i

PIK3CA

AKT

Immune checkpoint

New agents

antibody drug conjugates

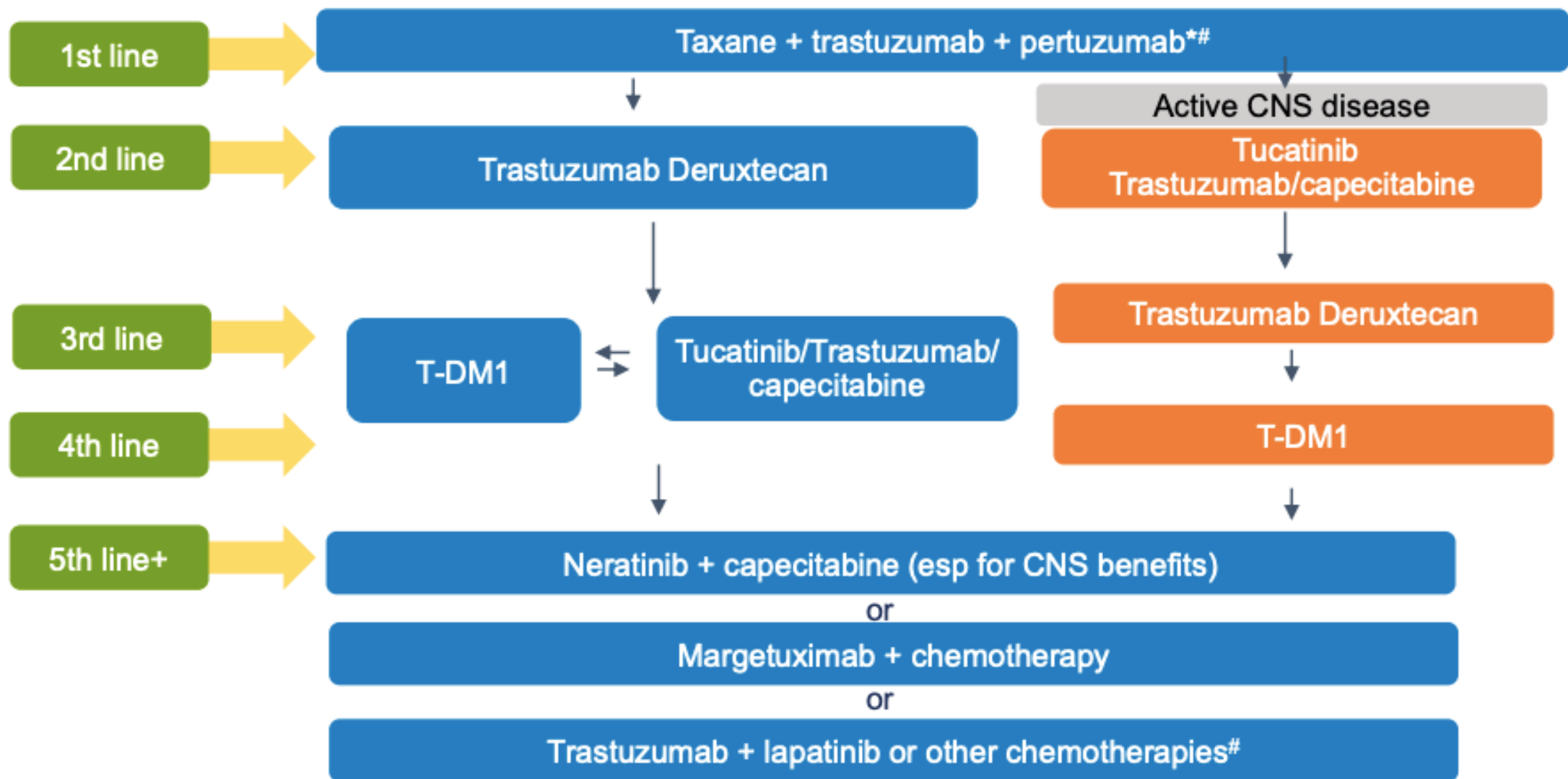
anti-HER2 antibody

TKI

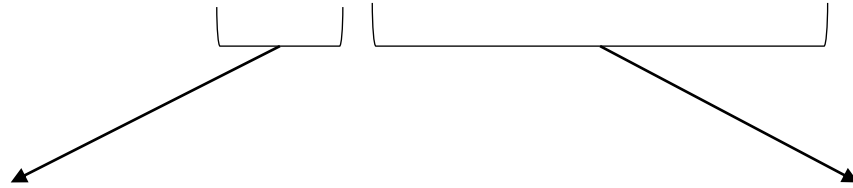
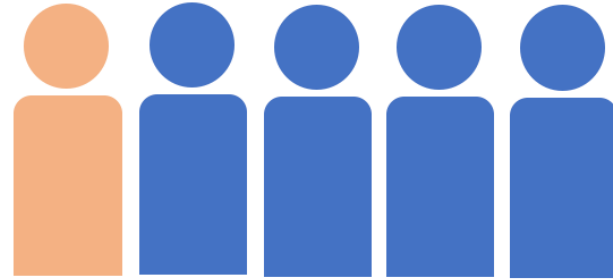
What is the best treatment sequence?

Stop HER2

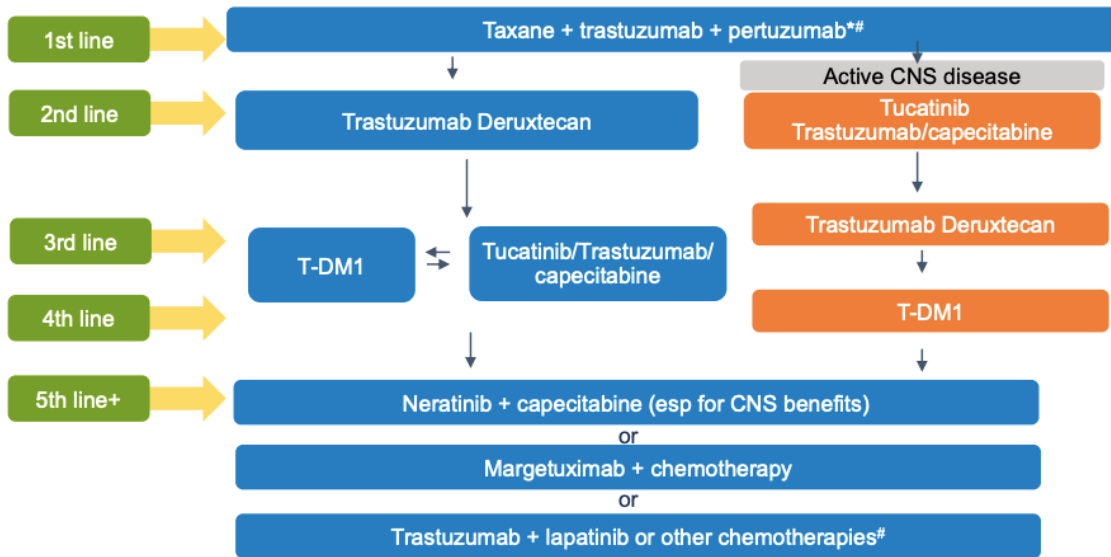
A 2022 Approach to Therapy for Metastatic HER2+ BC:



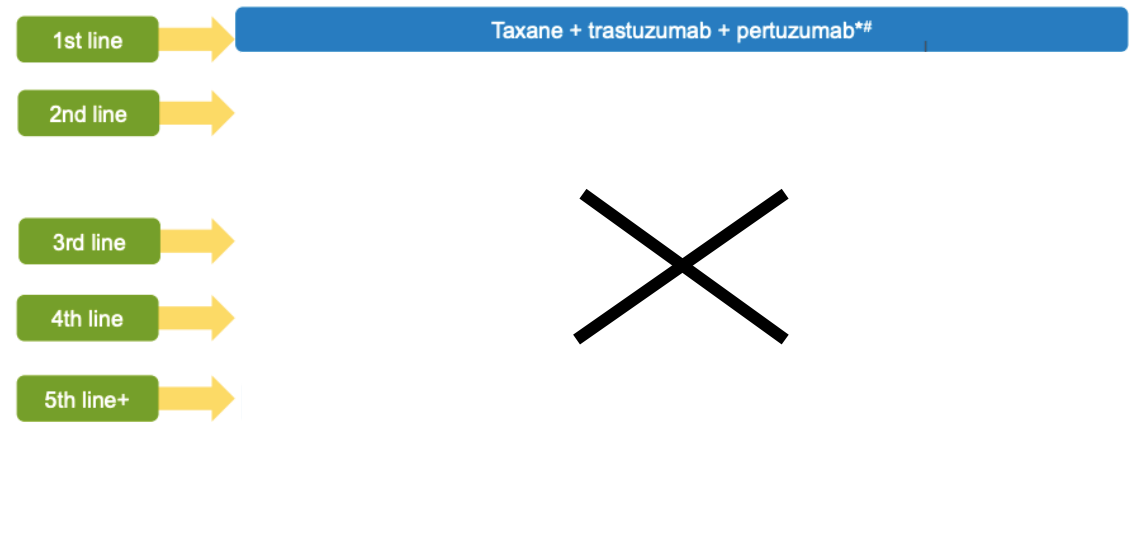
*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC



A 2022 Approach to Therapy for Metastatic HER2+ BC:



A 2022 Approach to Therapy for Metastatic HER2+ BC:



Algoritmo do tratamento do câncer de mama metastático HER2+ em 2023

Câncer de mama avançado HER2+ vem apresentando melhora do prognóstico em função dos tratamentos

Primeira linha ainda permanece: taxano, trastuzumabe e pertuzumabe

Segunda linha: trastuzumabe deruxtecan

Evidência do benefício da manutenção do bloqueio da via HER2

Desafio na incorporação dos benefícios para toda a população