Memorial Sloan Kettering Cancer Center

Metastatic HER2 + Breast Cancer: Current Landscape

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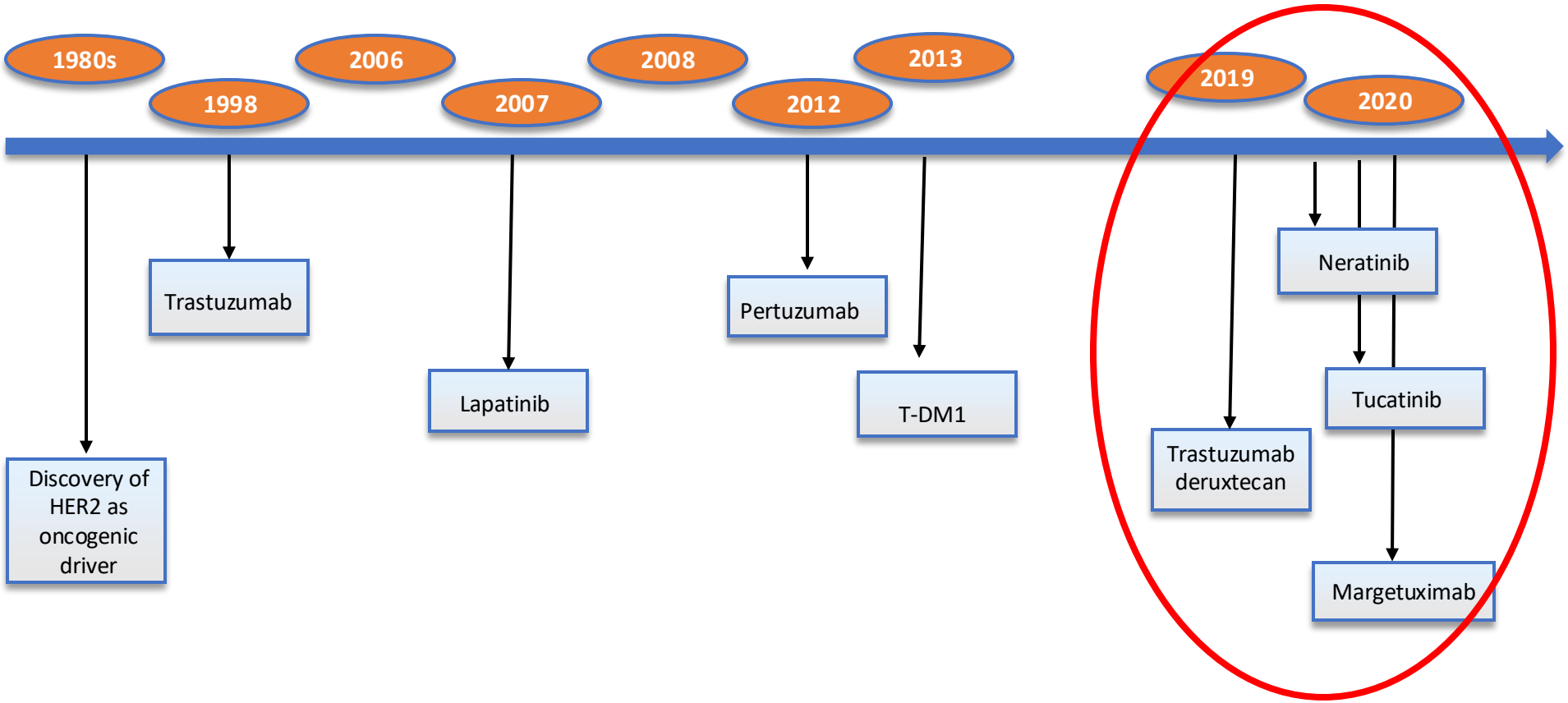
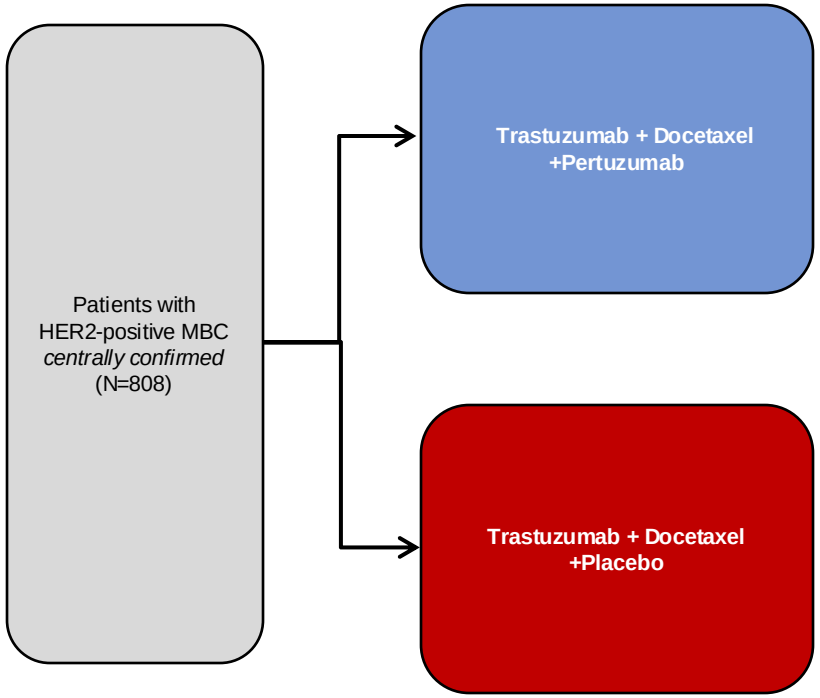
HER2-Targeted Therapies for MBC Timeline

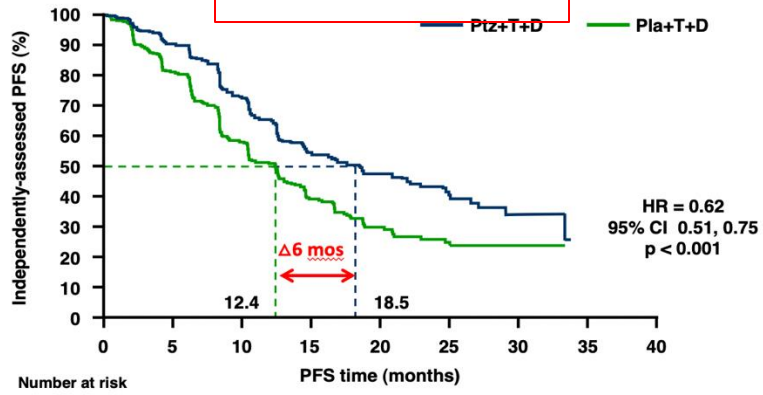


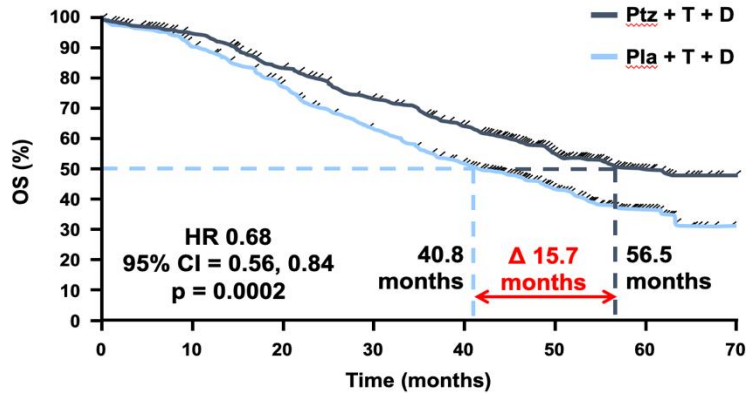
1st-Line

CLEOPATRA Trial :
Adding Pertuzumab to Docetaxel +Trastuzumab Improves PFS & OS



PFS
12.4 vs 18.5 m
P < 0.001

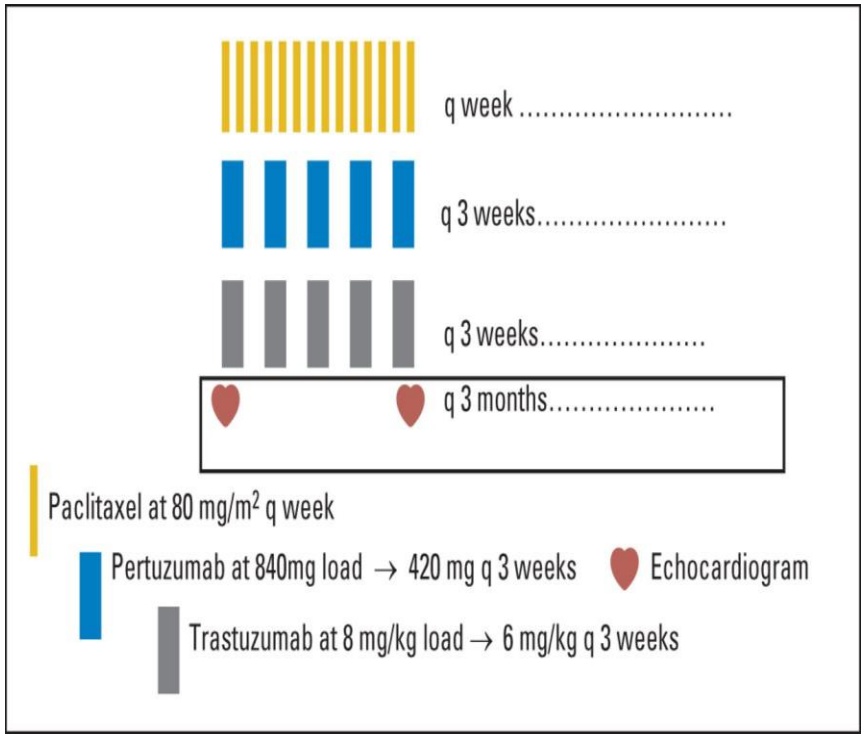


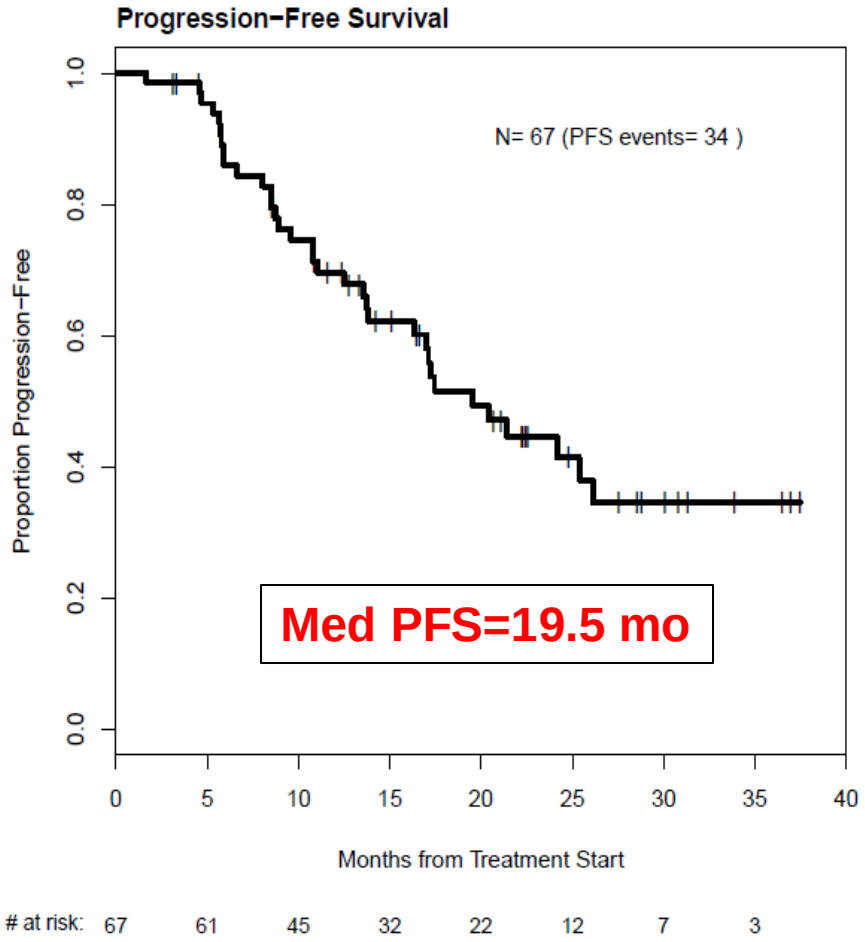


OS
40.8 vs 56.5 m
P = 0.0002

Baselga J et al, NEJM 2012; Swain S et al, NEJM 2015

NCCN/ASCO Guidelines: Preferred 1st line: Taxane + Trastuzumab+ Pertuzumab



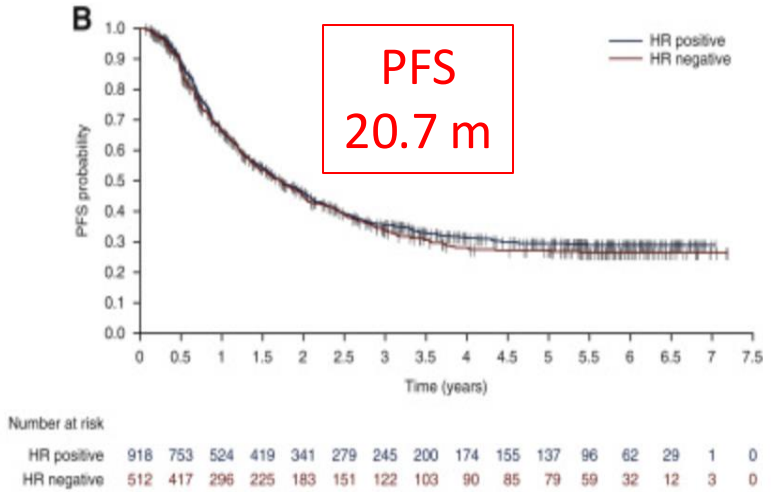


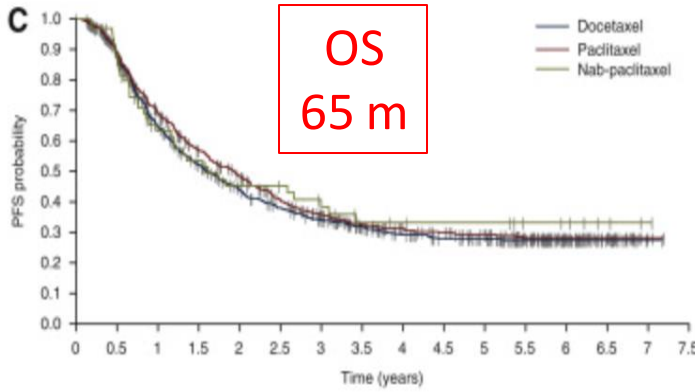
1.http://www.nccn.org/professionals/physician_gls/pdf/breast.pdfJM
2. Giordano et al. JCO 2018
3. Dang et al. JCO 2015

PERUSE: 1st Line Trastuzumab/Pertuzumab + Taxane in HER2+ MBC
Choice of docetaxel, paclitaxel or nab-paclitaxel

Median PFS was 20.7m and similar regardless of taxane backbone or HR status

Median OS was 65 m and was similar regardless of taxane; it was longer for HR+ cases, lending support for the use of maintenance ET

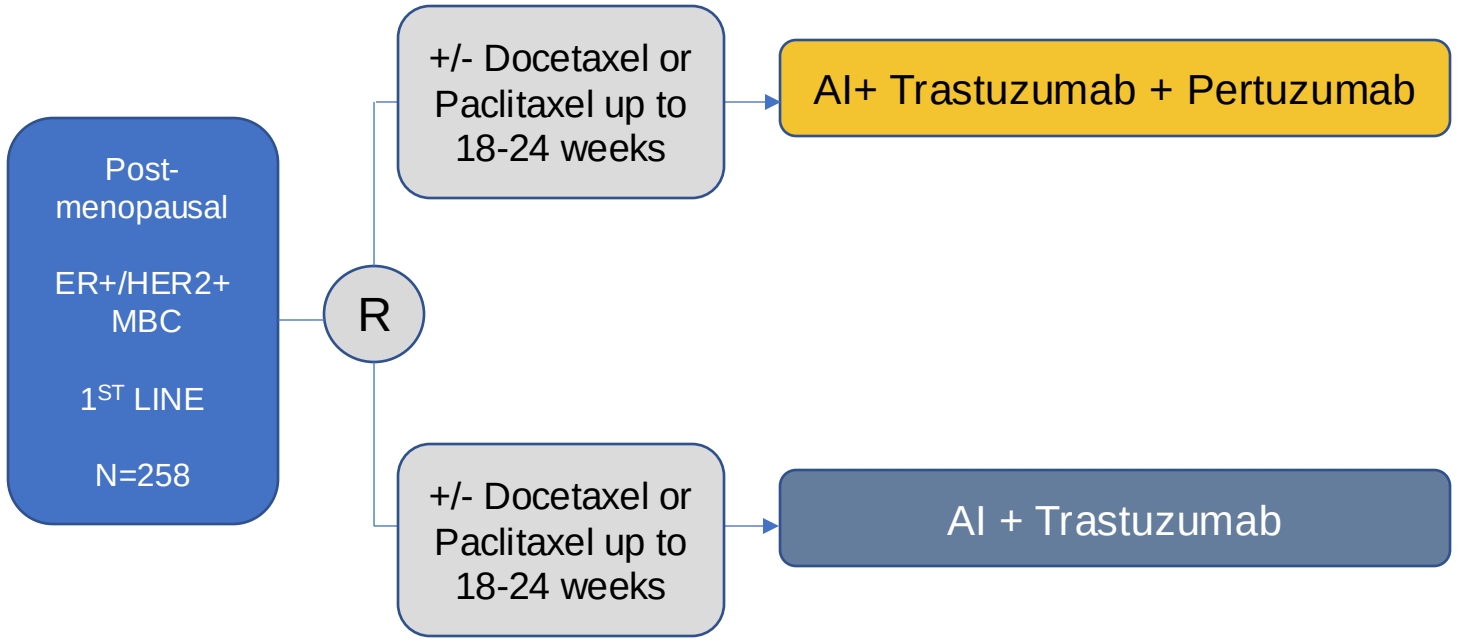




N=1436; Median f/u approx. 6 yrs

Miles D et al, Ann of Oncol 2021

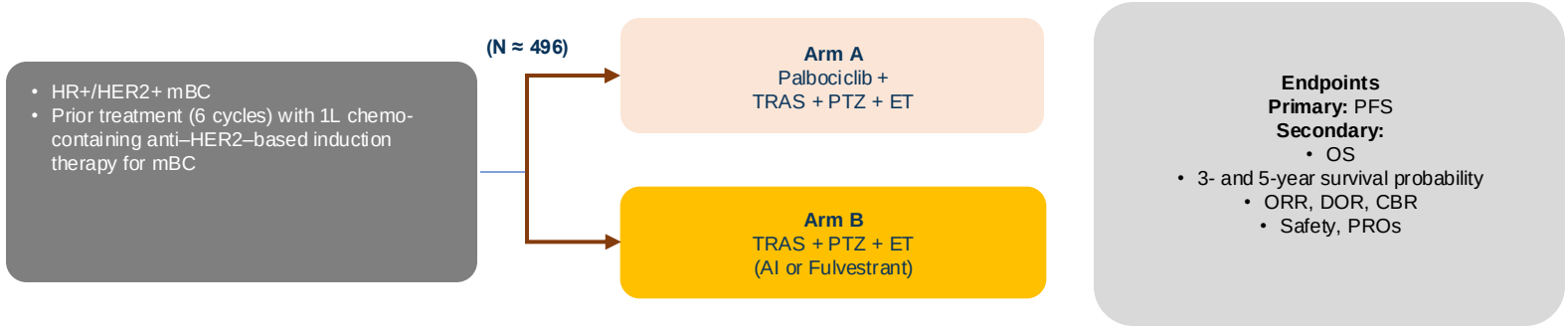
Can HR+ HER2+ MBC be treated without chemotherapy?
PERTAIN 1st Line Trial: Phase 2 Study for HR+ HER2+ MBC



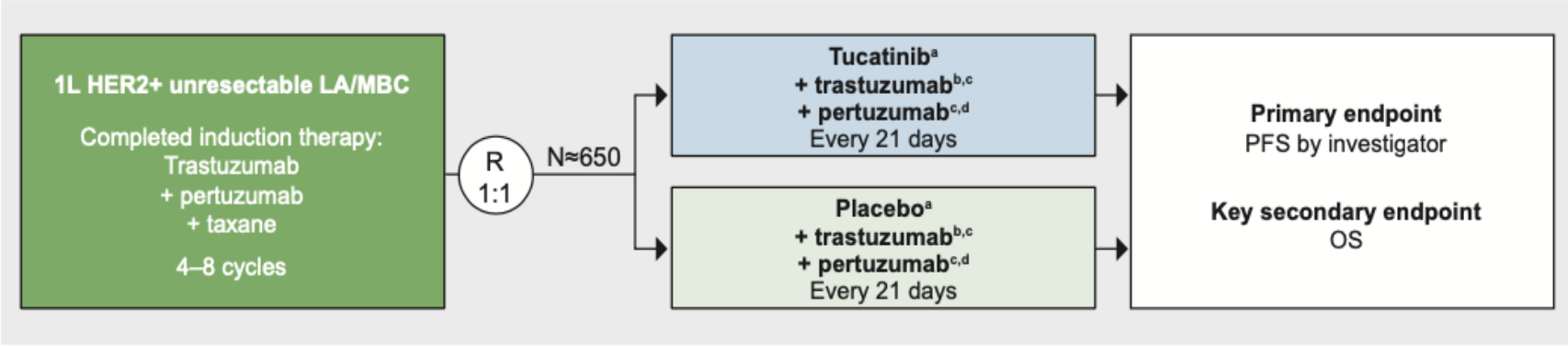
Rimawi M et al, JCO 2018

Randomized Phase 3 Trials in the Trastuzumab/Pertuzumab Maintenance Setting in HER2+ MBC

PATINA TRIAL



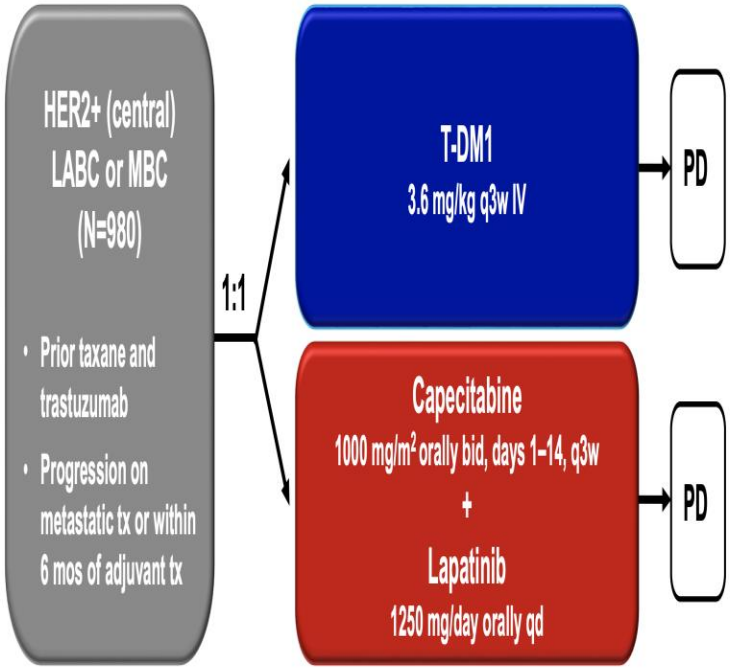
HER2CLIMB-05 TRIAL

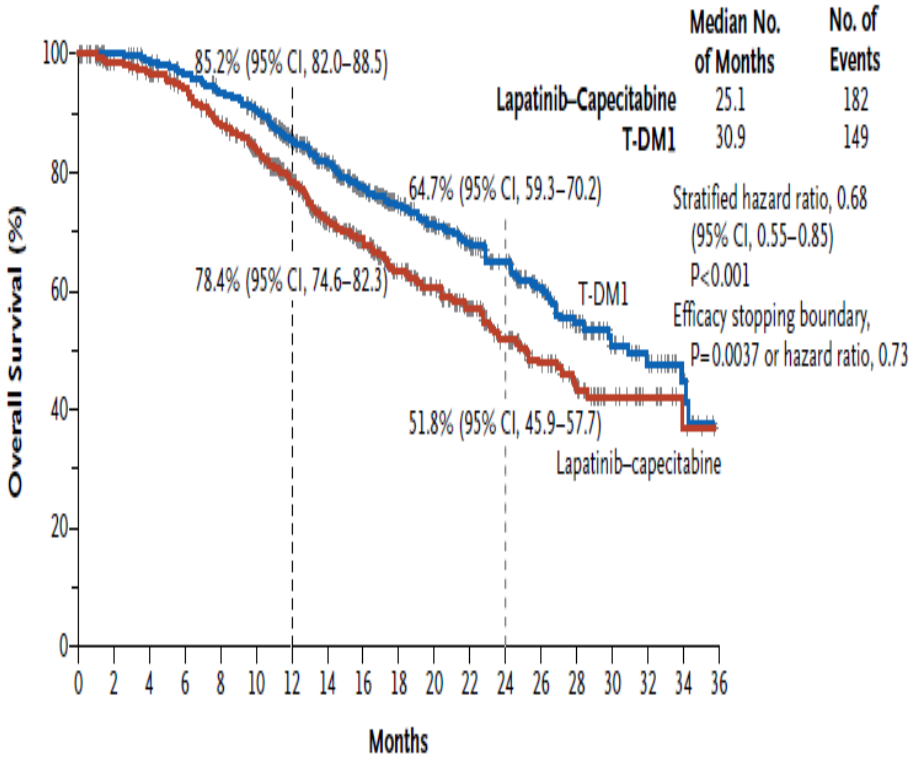


2nd-Line

EMILIA: TDM1 superior to Capecitabine+Lapatinib in HER2+ MBC

OS
25.1 m vs 30.9 m
HR 0.68





2013 Standard of Care 2nd Line Therapy

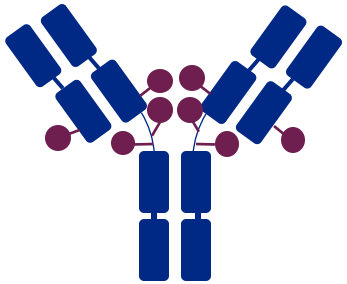
Verma S et al, NEJM 2012

Trastuzumab Deruxtecan (T-DXd): a Novel HER2 ADC

Characteristic Differences Between T-DXd and T-DM1

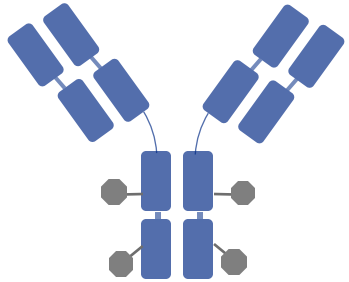
HER2 Targeting ADCs with similar mAB Backbone

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.

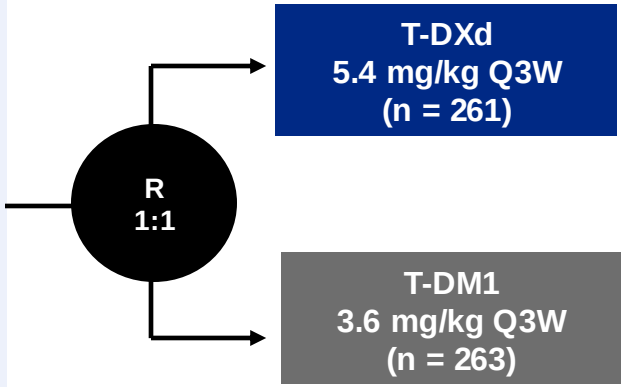
Cortes, J et al. ESMO 2021

DESTINY Breast-03: 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

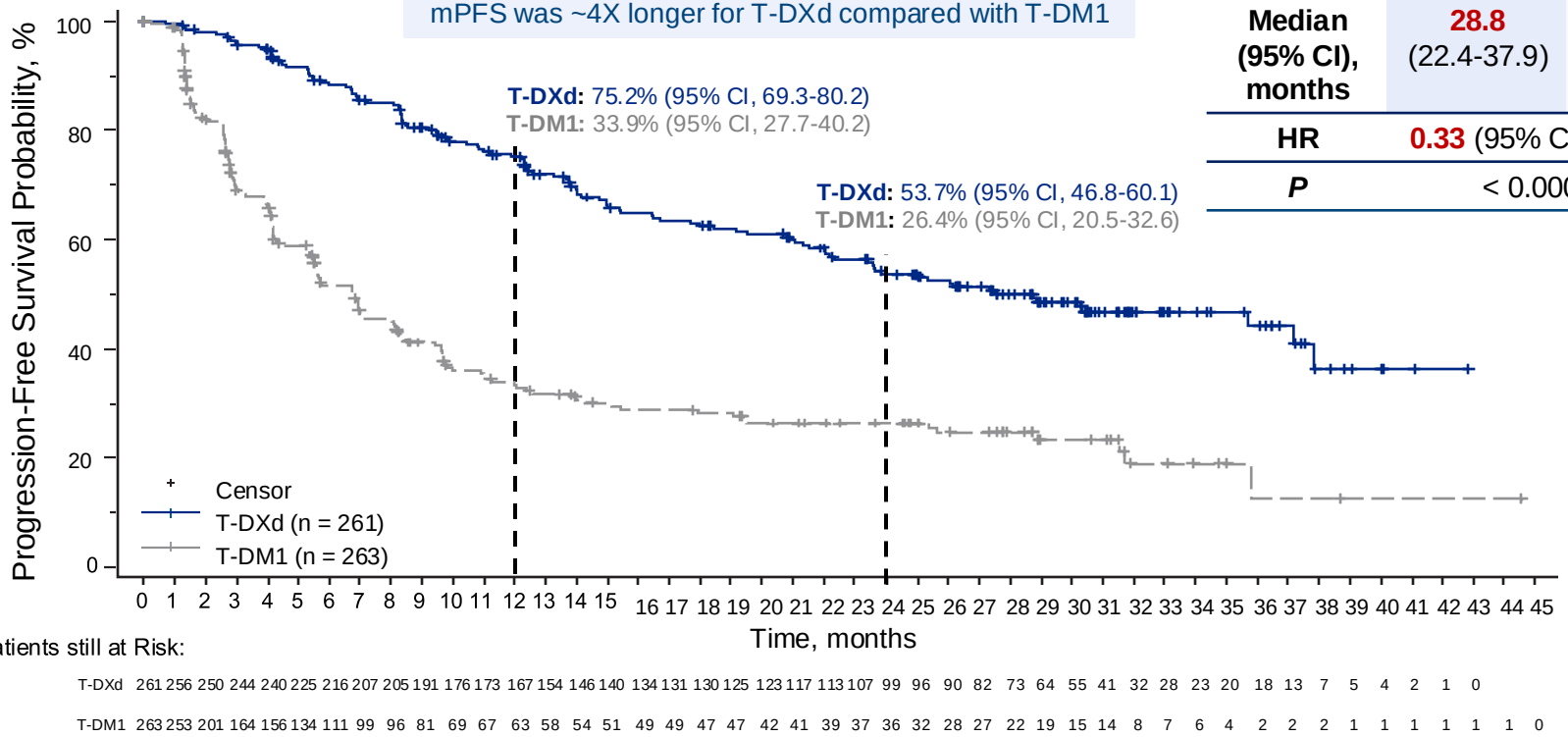
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

Cortes, J et al. ESMO 2021

DB-03 Updated Primary Endpoint: PFS

PFS
28.8 m vs 6.8 m

mPFS was ~4X longer for T-DXd compared with T-DM1

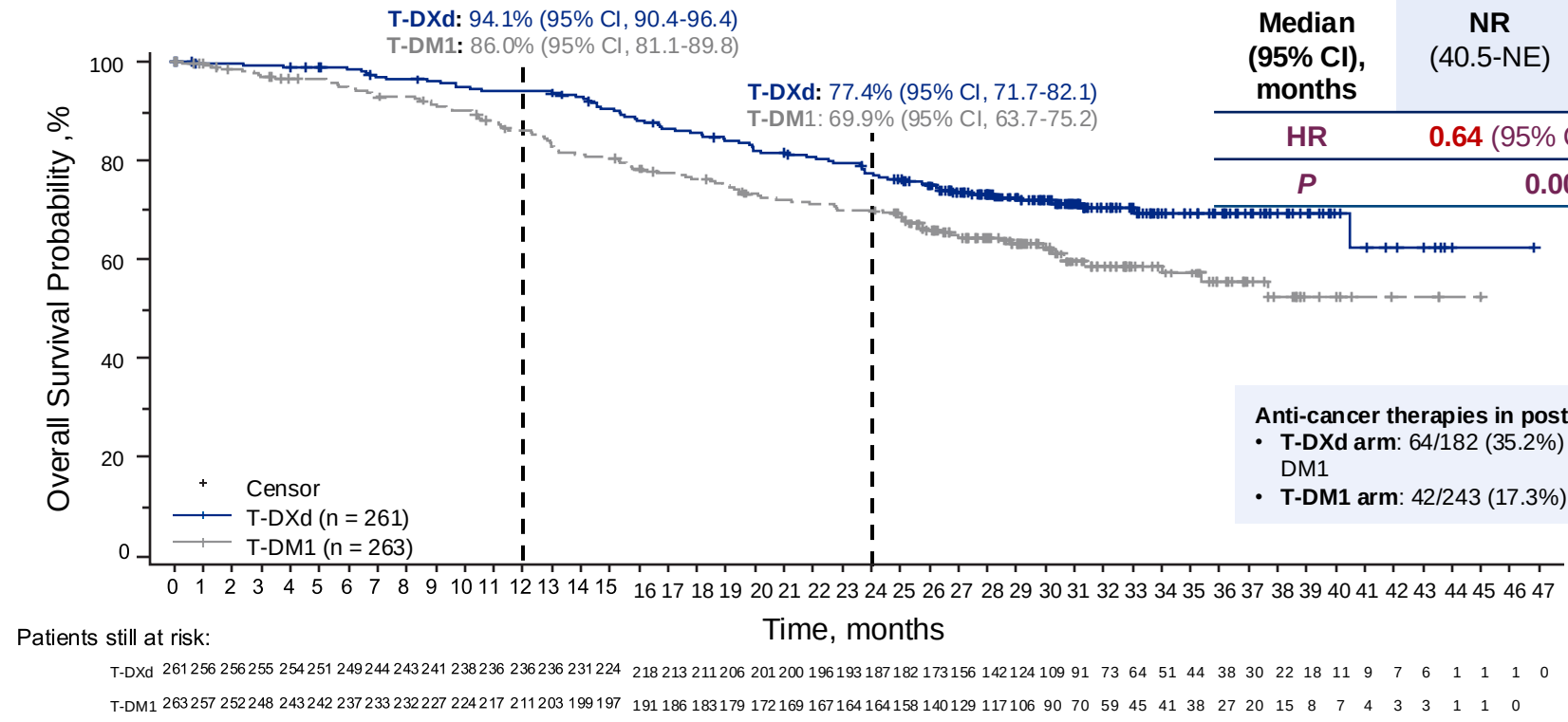


	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	**0.33** (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	

Hurvitz S et al, SABC 2022
Hurvitz S. et al. Lancet Onc 2023

DB-03 Key Secondary Endpoint: Overall Survival

24 m OS
69.9% vs 77.4%



	T-DXd	T-DM1
Median (95% CI), months	**NR** (40.5-NE)	**NR** (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**0.0037**[a,b]	

Anti-cancer therapies in post trial setting:
- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

HR, hazard ratio; mOS, median overall survival; NE, not estimable; NR, not reached; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
There were 19 patients (7.3%) treated with T-DXd and 28 patients (10.6%) treated with T-DM1 who were lost to follow-up.
[a]The *P* value for overall survival crossed the prespecified boundary (*P* = 0.013) and was statistically significant. [b]Two-sided from stratified log-rank test.

T-DXd preferred 2nd line Rx !

Hurvitz S et al, SABC 2022
Hurvitz S. et al. Lancet Onc 2023

DESTINYBreast-03 Incidence of Adjudicated ILD/Pneumonitis Events

CTCAE Grade Per Adjudication Committee	ENHERTU (n = 257)	T-DM1 (n = 261)
Adjudicated as study drug-related ILD/pneumonitis, n (%)		
Any grade	39 (15.2)	8 (3.1)
1	11 (4.3)	4 (1.5)
2	26 (10.1)	3 (1.1)
3	2 (0.8)	1 (0.4)
4	0	0
5	0	0

Drug-Related ILD (DILD) Results

- Adjudicated DILD/pneumonitis rates were similar to other mBC trials with ENHERTU
- ENHERTU had a higher overall DILD/pneumonitis incidence (15.2%) versus T-DM1 (3.1%)
- Majority of events (94.9%; n = 37/39) were grade 1 or 2, and the overall incidence of grade 3 adjudicated DILD/pneumonitis was 0.8% in the ENHERTU arm
- No grade 4/5 adjudicated DILD/pneumonitis was reported in either arm

CTCAE, Common Terminology Criteria for Adverse Events; **DILD,** drug-related interstitial lung disease; **ILD,** interstitial lung disease; **mBC**, metastatic breast cancer; **T-DM1,** ado-trastuzumab emtansine.

Daiichi-Sankyo

DESTINY Breast 07

Study design

DESTINY-Breast07: a Phase 1b/2, multicenter, open-label, two-part, modular study (NCT04538742)

PATIENT POPULATION

- Locally assessed HER2+ (IHC 3+, IHC 2+/ISH+) advanced/mBC, with measurable disease per RECIST 1.1
- Either no brain metastases or previously treated stable brain metastases
- ECOG PS of 0 or 1

Prior lines of therapy

- No prior therapy for mBC was allowed
- A disease-free interval of ≥12 months from adjuvant HER2-directed therapy or chemotherapy was required
- Prior taxane, trastuzumab, and pertuzumab exposure was allowed in the (neo)adjuvant setting

This is the first dataset of T-DXd monotherapy and T-DXd + pertuzumab as first-line treatment for HER2+ mBC

Randomized

Module 0: T-DXd monotherapy (n=75)
(T-DXd 5.4 mg/kg IV Q3W)*

Module 1: T-DXd + durvalumab

Module 2: T-DXd + pertuzumab (n=50)
(T-DXd 5.4 mg/kg IV Q3W + pertuzumab 420 mg IV Q3W, with an 840-mg loading dose)†

Stratification factors

- HR status
- Disease status
- PD-L1 status

Endpoints for the Part 2 dose-expansion phase

Primary
Safety and tolerability, including AEs and SAEs

Key secondary
ORR, PFS (evaluated by investigator per RECIST 1.1), and DOR

DCO: December 22, 2023‡

Results reported here are from an interim analysis of the Part 2 dose-expansion phase for Modules 0 and 2 only; the Part 1 dose-finding phase of the study has been described previously[1]

*Patients in Module 0 received the approved T-DXd dose for HER2+ breast cancer; †patients received the RP2D from the study's dose-finding phase; ‡the corresponding abstract reported data from the August 1, 2023, DCO
AE, adverse event; DCO, data cutoff; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; IHC, immunohistochemistry; ISH+, in situ hybridization–positive; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RP2D, recommended Phase 2 dose; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

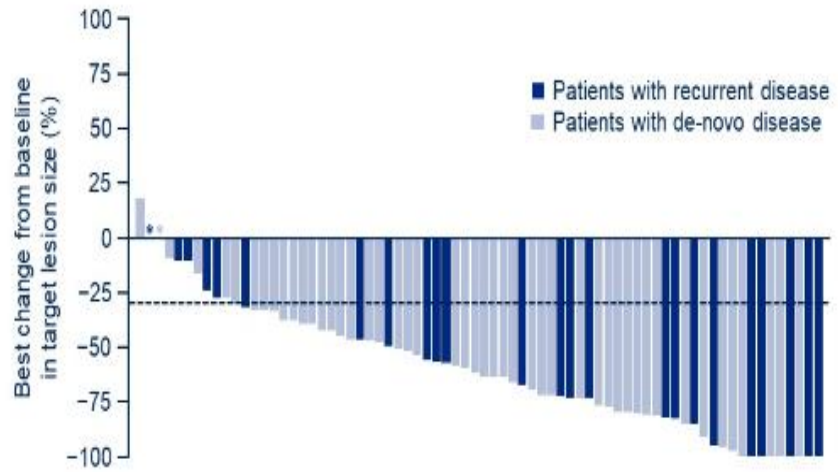
1. André F, et al. Poster presented at ASCO 2022 (Abstract 3025)

PRESENTED BY: Fabrice André, MD, PhD

DESTINY Breast 07

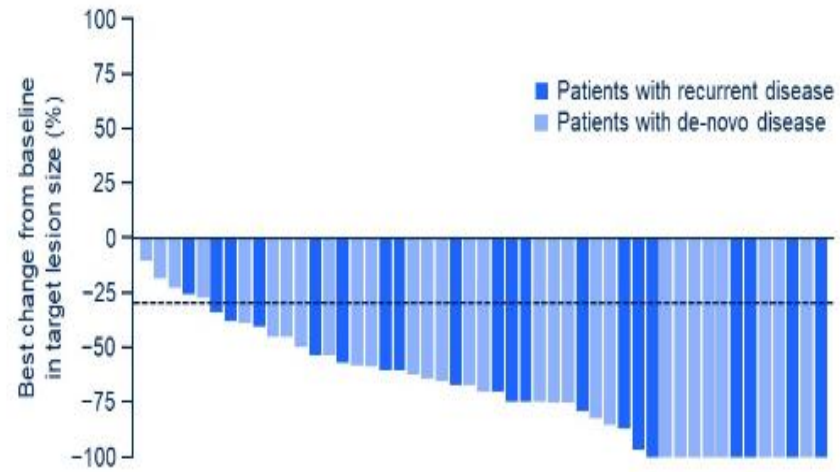
Response to treatment per RECIST 1.1 by investigator

T-DXd monotherapy (n=75)



Confirmed ORR, % (80% CI)	76.0 (68.5–82.4)
Complete response, n (%)	6 (8.0)
Partial response, n (%)	51 (68.0)
Median DOR, months (range)	NE (2.1–28.5)

T-DXd + pertuzumab (n=50)

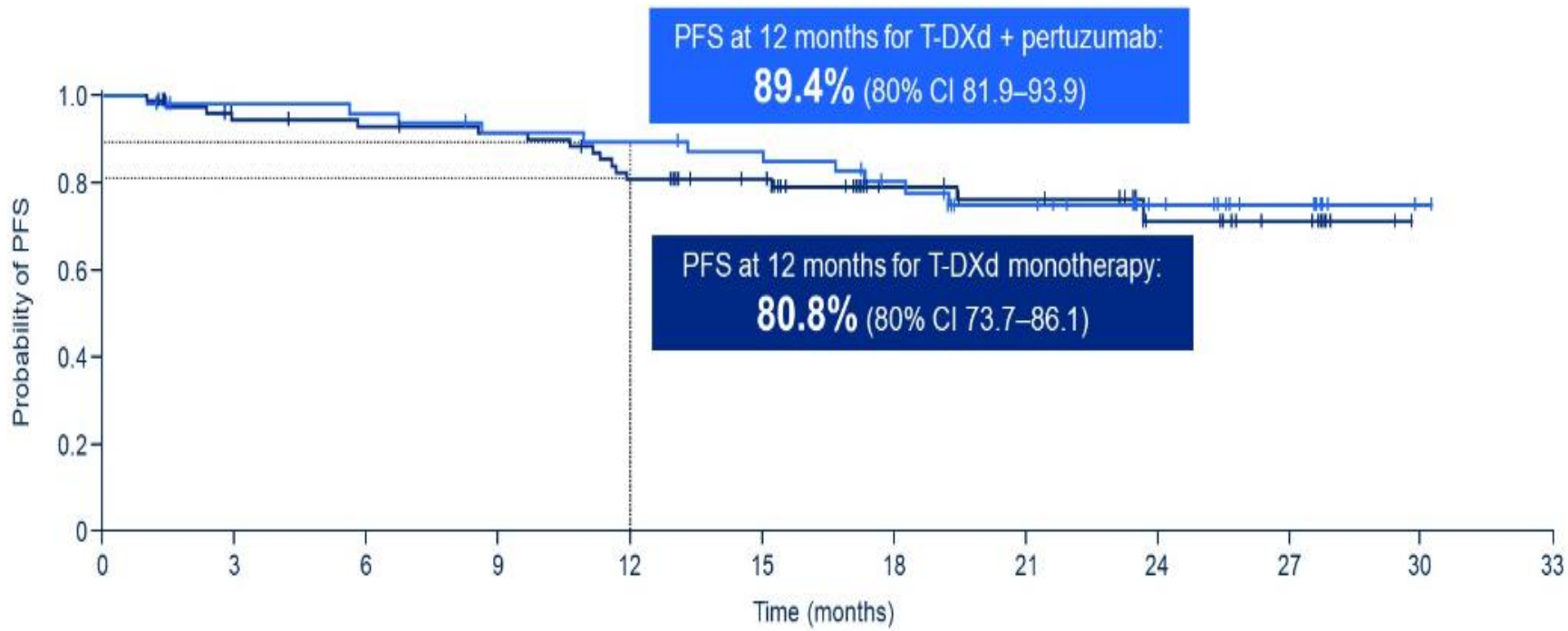


Confirmed ORR, % (80% CI)	84.0 (75.3–90.5)
Complete response, n (%)	10 (20.0)
Partial response, n (%)	32 (64.0)
Median DOR, months (range)	NE (4.5–28.3)

Dashed reference line at −30% indicates the threshold for partial response
Responses are captured for patients with baseline data and at least one follow-up assessment
DCO was December 22, 2023. Median duration of follow up was 23.9 months for T-DXd monotherapy and 25.3 months for T-DXd + pertuzumab
*Patients had 0% change from baseline
CI, confidence interval; DCO, data cutoff; DOR, duration of response; NE, not evaluable; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

DESTINY Breast 07

Progression-free survival



Number at risk												
T-DXd monotherapy	75	65	63	61	53	47	27	24	13	8	0	0
T-DXd + pertuzumab	50	46	45	42	41	38	31	23	13	7	1	0

Number of randomized patients / number of events	
T-DXd monotherapy	75 / 16
T-DXd + pertuzumab	50 / 11

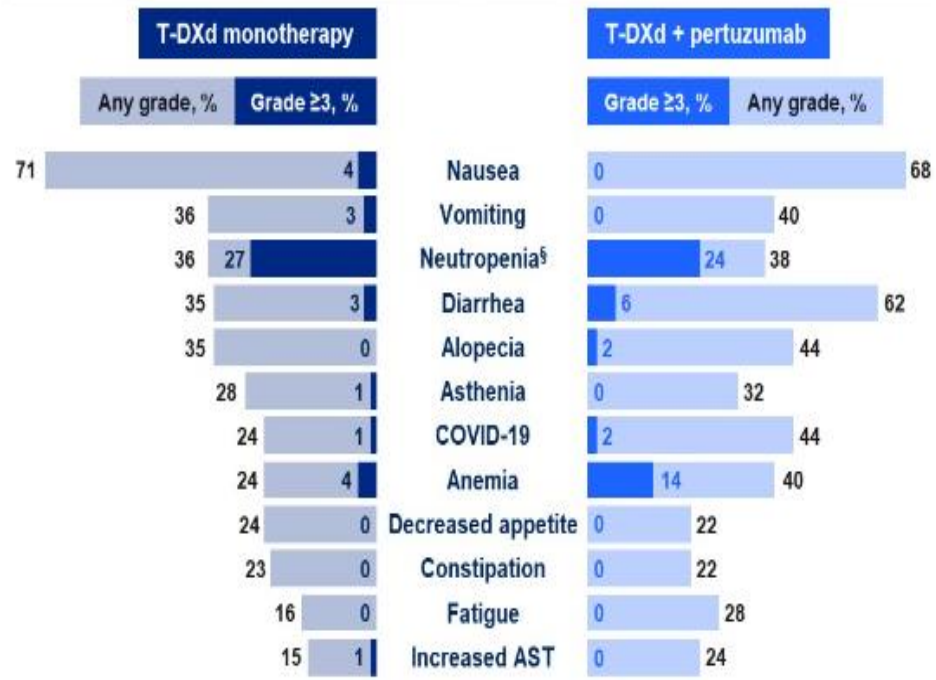
The number of PFS events is small, and most patients were censored
DCO was December 22, 2023. Median duration of follow up was 23.9 months for T-DXd monotherapy and 25.3 months for T-DXd + pertuzumab
CI, confidence interval; DCO, data cutoff; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

DESTINY Breast 07

Safety overview

	T-DXd monotherapy (n=75)	T-DXd + pertuzumab (n=50)
Median actual treatment duration, months (range)*		
T-DXd	16.3 (0.7–30.9)	17.8 (0.9–30.7)
Pertuzumab	N/A	17.6 (0.9–30.7)
Any AE, n (%)	75 (100)	50 (100)
Any AEs Grade ≥3, n (%)	39 (52.0)	31 (62.0)
AEs associated with drug interruptions of T-DXd, n (%)	44 (58.7)	32 (64.0)
AEs associated with dose reduction of T-DXd, n (%)	12 (16.0)	8 (16.0)
AEs associated with discontinuation of T-DXd, n (%)†	8 (10.7)	8 (16.0)
Any SAEs, n (%)	13 (17.3)	13 (26.0)
AEs leading to death, n (%)	1 (1.3)‡	0
AESIs, n (%)		
Pneumonitis (adjudicated as ILD related to T-DXd)	7 (9.3)	7 (14.0)
Grade 1	2 (2.7)	0
Grade 2	5 (6.7)	6 (12.0)
Grade 3	0	1 (2.0)
LV dysfunction (possibly related to T-DXd)	5 (6.7)	2 (4.0)

Any-grade AEs (>20% of patients in either module) with incidence of Grade ≥3 events



Grade 2 diarrhea events were reported in:
- **13.3%** of patients in the **T-DXd monotherapy** module
- **32.0%** of patients in the **T-DXd + pertuzumab** module

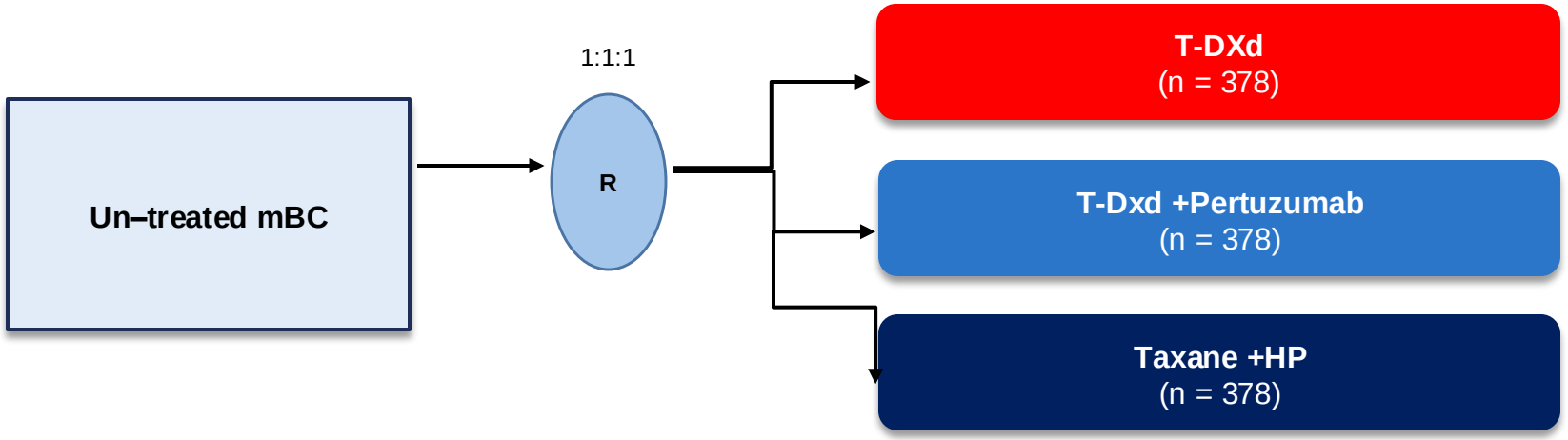
DCO was December 22, 2023

*Total treatment duration, excluding dose delays; †discontinuation of T-DXd due to toxicities resulted in the discontinuation of pertuzumab until resolved; ‡reported by investigator as non-treatment-related post-acute COVID-19 syndrome; §grouped term including neutropenia, decreased neutrophil count, and febrile neutropenia events

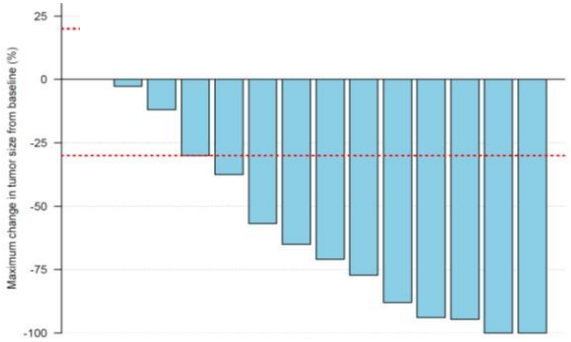
AE, adverse event; AESI, adverse event of special interest; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; DCO, data cutoff; ILD, interstitial lung disease; LV, left ventricular; N/A, not applicable; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

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

Primary Endpoint: PFS

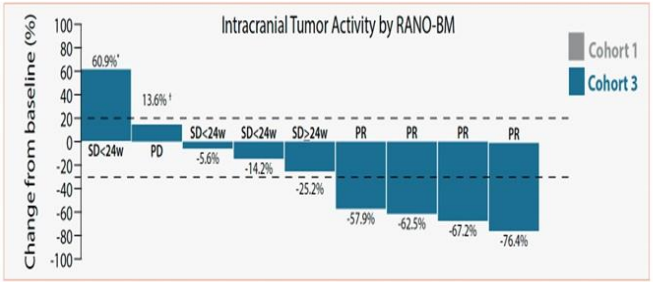


CNS Activity of TDXd in Pts with HER2+ Breast Cancer Brain Metastases



TUXEDO-1 trial
Bartsch et al, ESMO Breast 2022

ORR-IC = **73%** in pts with active BM



DEBBRAH trial
Vaz Batista et al, SABCS 2021

ORR-IC =**44%** in pts with Active BM

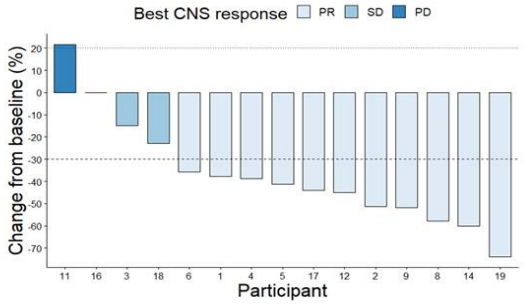


Figure 5 : Best CNS response to T-DXd. Waterfall plot of best CNS response in participants with measurable disease (n = 15). PR = partial response

DFCI/Duke/MDACCC series
Kabraji et al, SABCS 2021

ORR-IC =**73%**
(70% in pts with active BM)

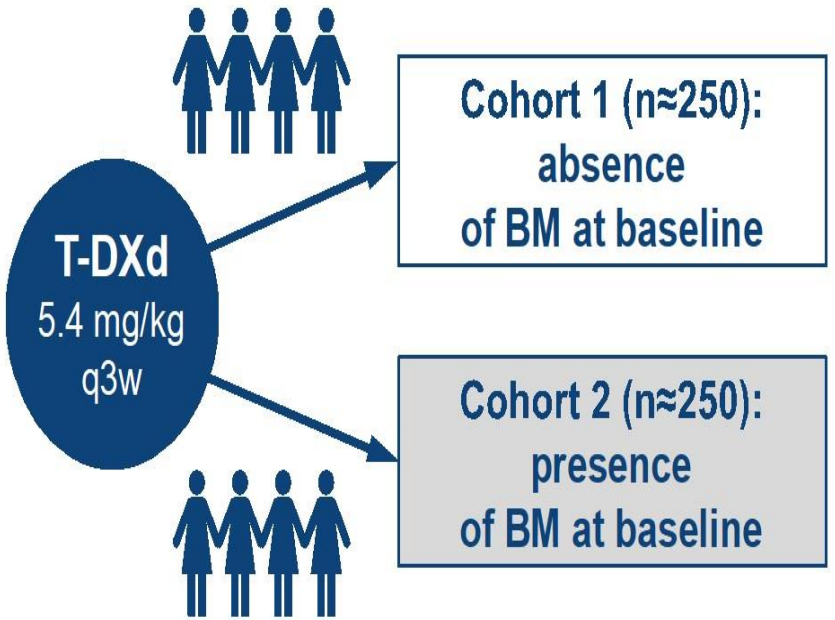
Lin N et al. ASCO 2022

DESTINY-Breast12

Study Design and Population

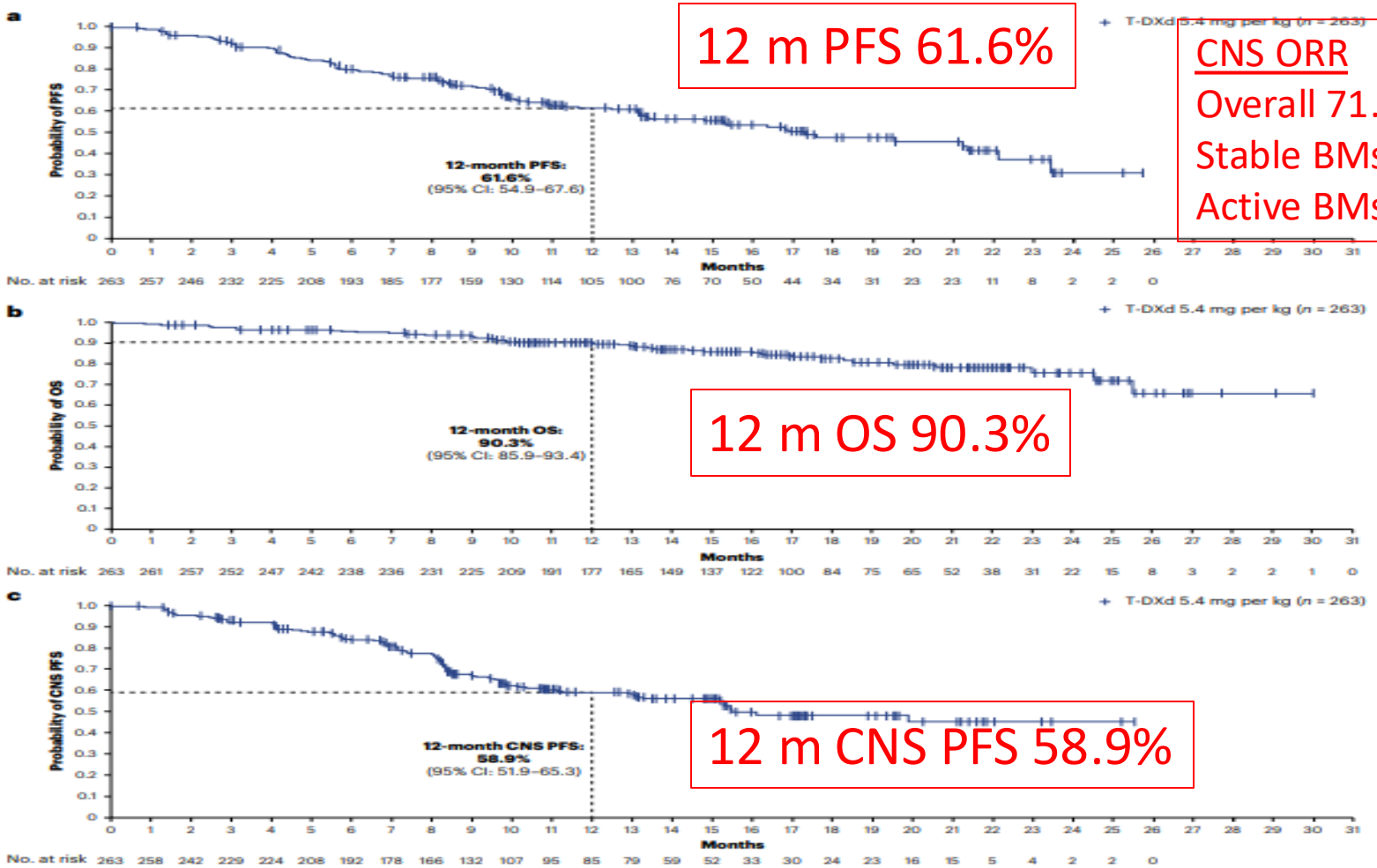
Patient population (N≈500)

- HER2-positive advanced or metastatic breast cancer
- Absence or presence of BM at baseline
- ≤2 prior lines of therapy in the metastatic setting



Lin et al. ESMO 2024

12 month PFS, OS and CNS PFS



12 m PFS 61.6%

CNS ORR
Overall 71.7%
Stable BMs 79.2%
Active BMs 62.3%

12 m OS 90.3%

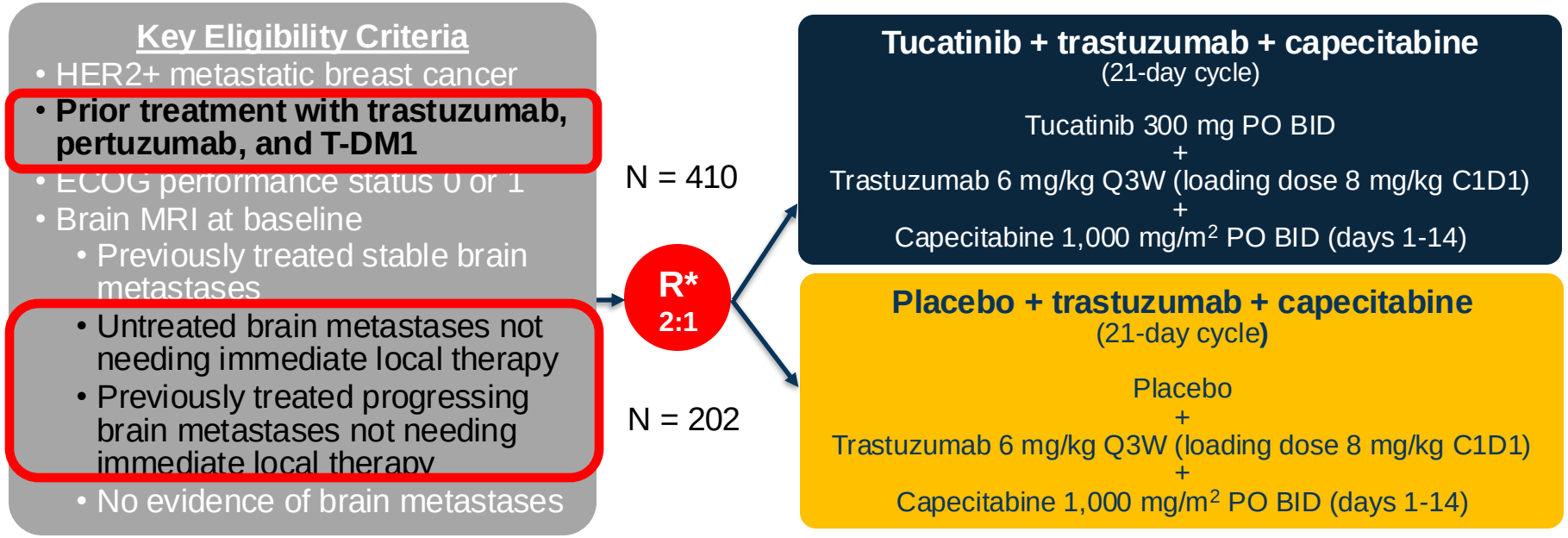
12 m CNS PFS 58.9%

Fig. 2 | Kaplan–Meier analysis of key efficacy endpoints in patients with baseline BMs. a, Overall PFS. **b**, OS. **c**, CNS PFS per RECIST 1.1 as assessed by ICR. Tick marks indicate censored data. Analysis was based on the full analysis set.

Harbeck et al. Nature Med 2024

3rd-Line

HER2 CLIMB: RANDOMIZED PHASE II TRIAL



Median lines for MBC: 3

Primary endpoint: PFS

*Stratification factors: presence of brain metastases (yes/no), Eastern Cooperative Oncology Group (ECOG) status (0 or 1), and region (United States or Canada or rest of world); MRI = magnetic resonance imaging; Q3W = every 3 weeks; Murthy R, et al. *N Engl J Med*. 2020;382(7):597-609.

HER2 CLIMB: Randomized Phase 2 Trial of Tucatinib

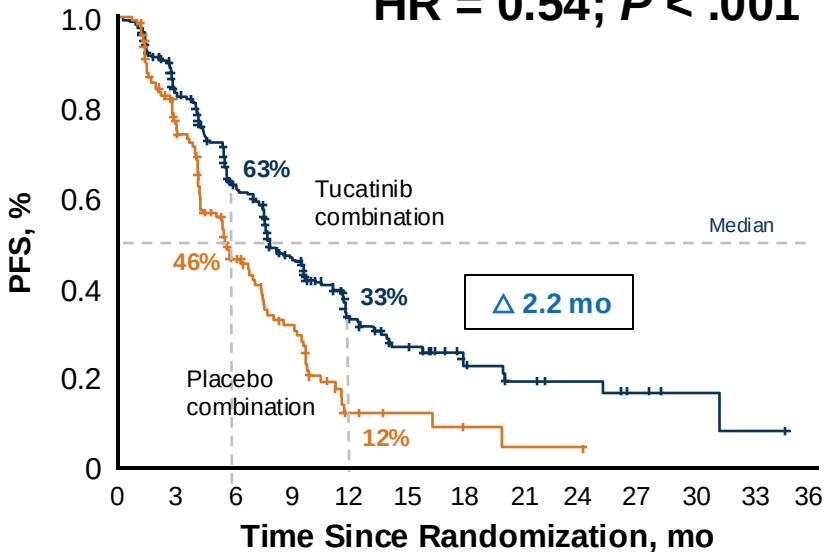
Median duration of followup of 14mo

Tucatinib Improves PFS and OS

Median PFS

7.8 mo vs 5.6 mo

HR = 0.54; *P* < .001

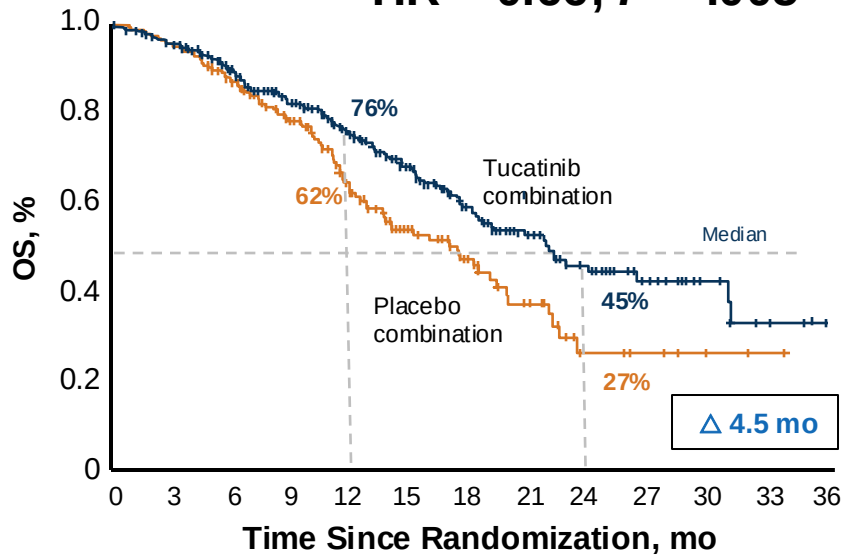


No. at Risk													
Tuc + tras + cape	320	235	152	96	40	29	15	10	8	4	2	1	0
Pbo + tras + cape	160	94	45	27	6	4	2	1	1	0	0	0	0

Median OS

21.9 mo vs 17.4 mo

HR = 0.66; *P* = .005

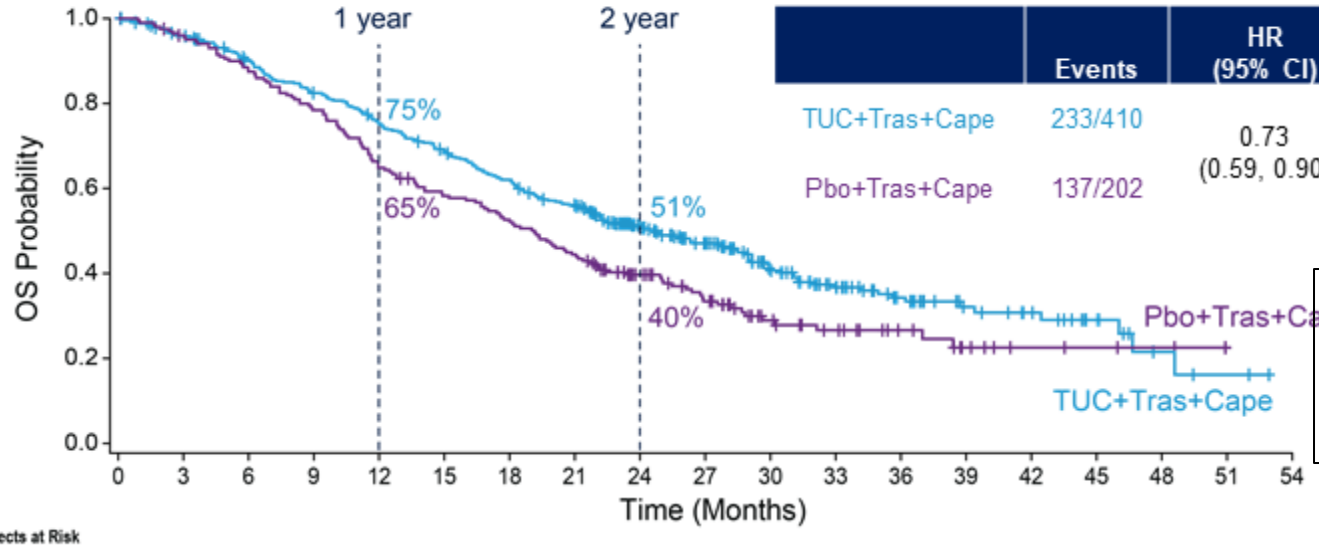


No. at Risk													
Tuc + tras + cape	410	388	322	245	178	123	80	51	34	20	10	4	0
Pbo + tras + cape	202	191	160	119	77	48	32	19	7	5	2	1	0

Murthy R, et al. *N Engl J Med*. 2020;382(7):597-609.

HER2CLIMB: Updated Overall Survival

Median follow-up 29.6 months



	Events	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)

OS
19.2 m vs 24.7 m
P =0.004

a Median overall study follow-up: 29.6 months

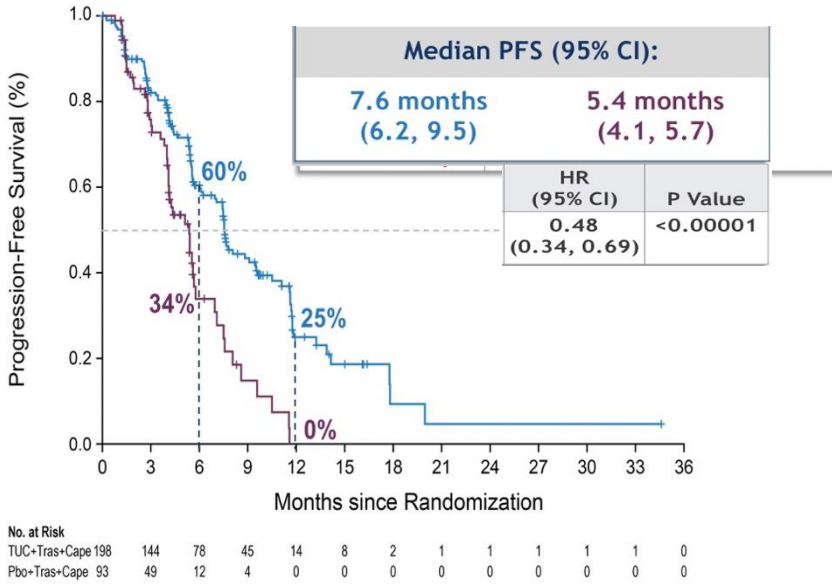
- OS benefit with tucatinib was maintained with longer follow-up, with a 5.5 month improvement in median OS in the tucatinib arm compared to the placebo arm.
- Sensitivity analyses accounting for cross-over showed consistent results with ITT analysis.

Curigliano G, Ann of Oncol 2022

HER2CLIMB: Patients with Brain Metastases

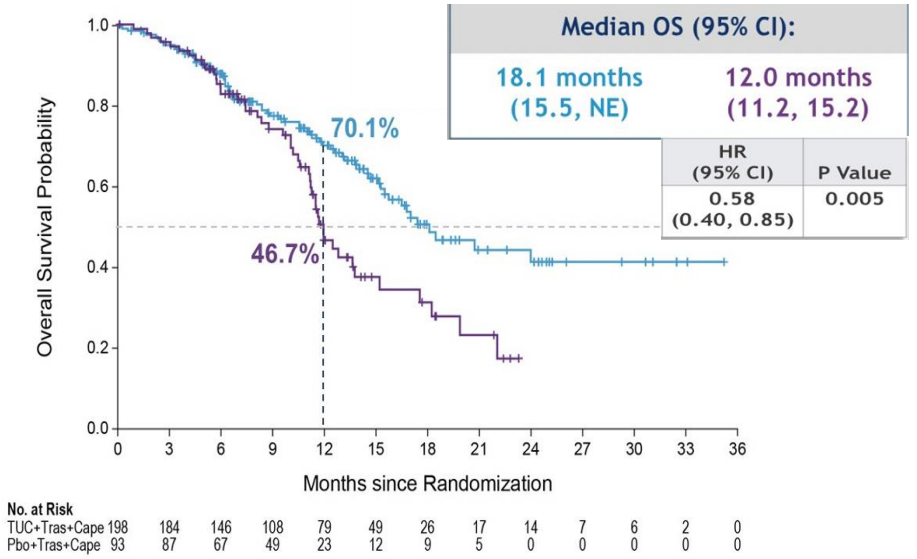
Secondary analyses

PFS
5.4 m vs 7.6 m
P < 0.00001



Risk of progression in patients with BM was reduced by 52%

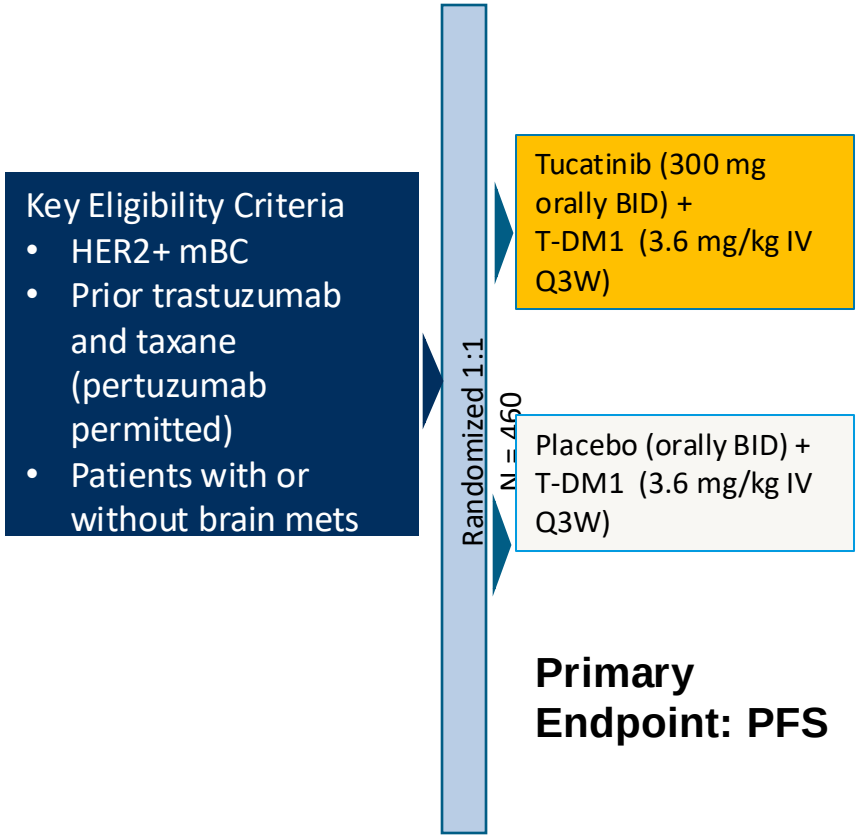
OS
12.0 m vs 18.1 m
P = 0.005



Risk of death in patients with BM was reduced by 42%

Murthy R et al. *N Engl J Med*. 2020;382:597-609.
Lin NU et al. *J Clin Oncol*. 38;2020:2610-2619

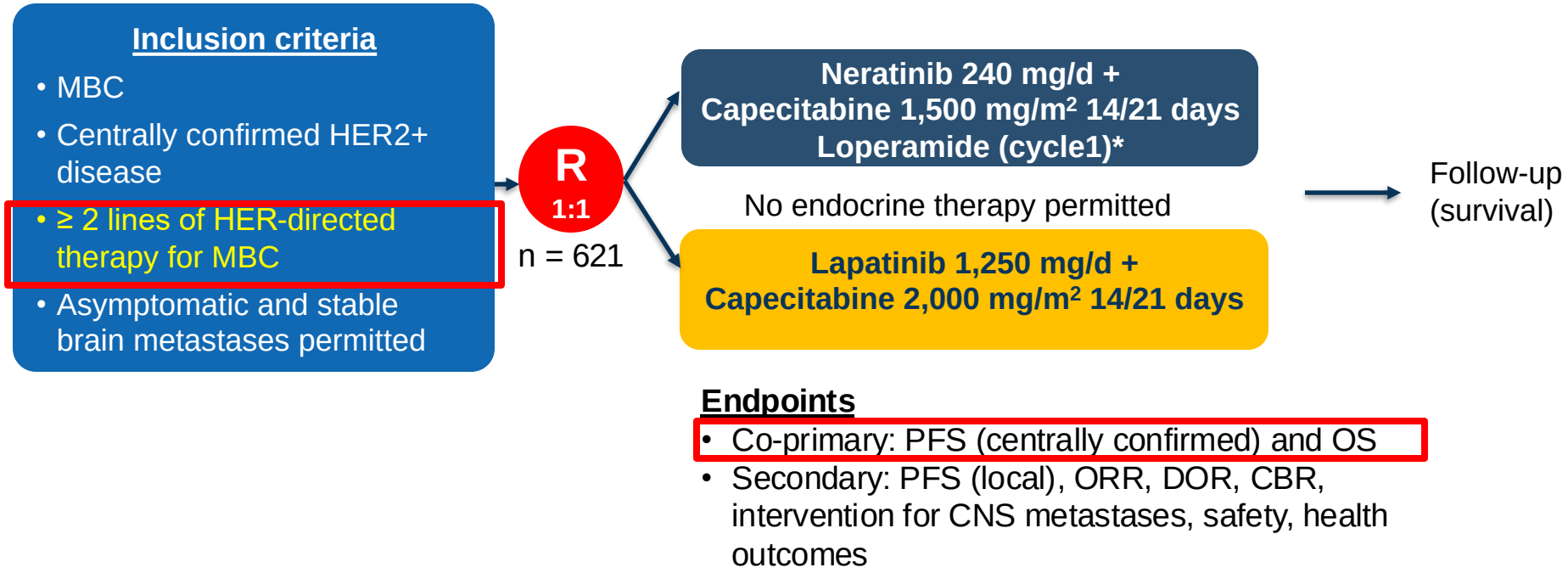
HER2 CLIMB-02



- Prior Rx
  - 88-91% had prior HP
- PFS
  - ITT
    - 7.4 m vs 9.5 m (HR 0.76, p 0.0163)
  - Brain mets
    - 5.7 m vs 7.8 m (HR 0.64)
- OS
  - Not reached vs 38m (HR 1.23)

Hurvitz et al. SABC 2023

NALA: Phase 3 Trial of Neratinib for HER2+ MBC

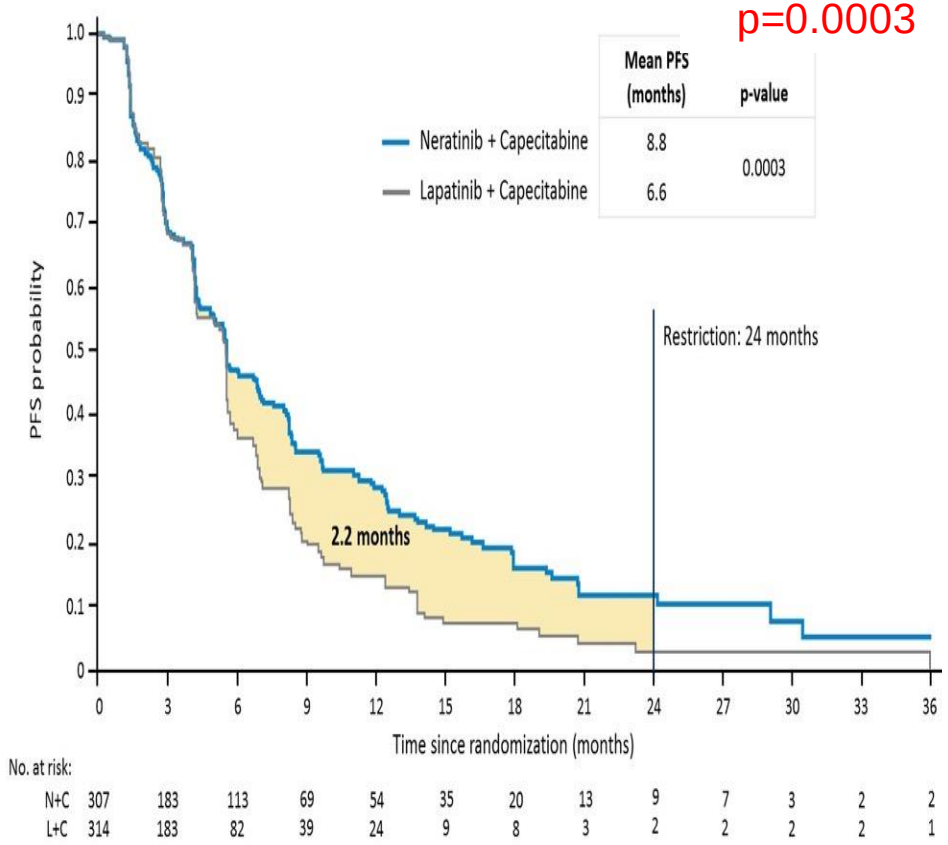


*Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 hours for the first 3 days, then loperamide 2 mg every 6-8 hours until end of cycle 1; thereafter as needed; Saura C, et al. J Clin Oncol 2020 Sep 20;38(27):3138-3149.

NALA: Co-primary endpoints of PFS and OS

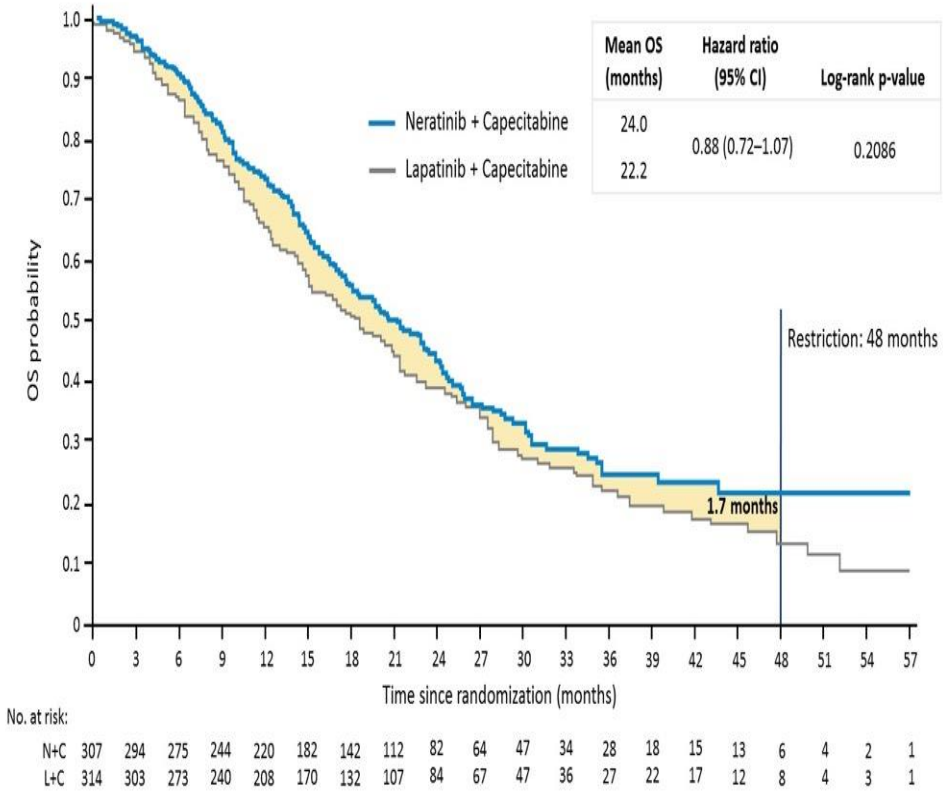
Centrally confirmed PFS

8.8 vs 6.6 mo
Δ 2.2 mo
p=0.0003



Overall Survival

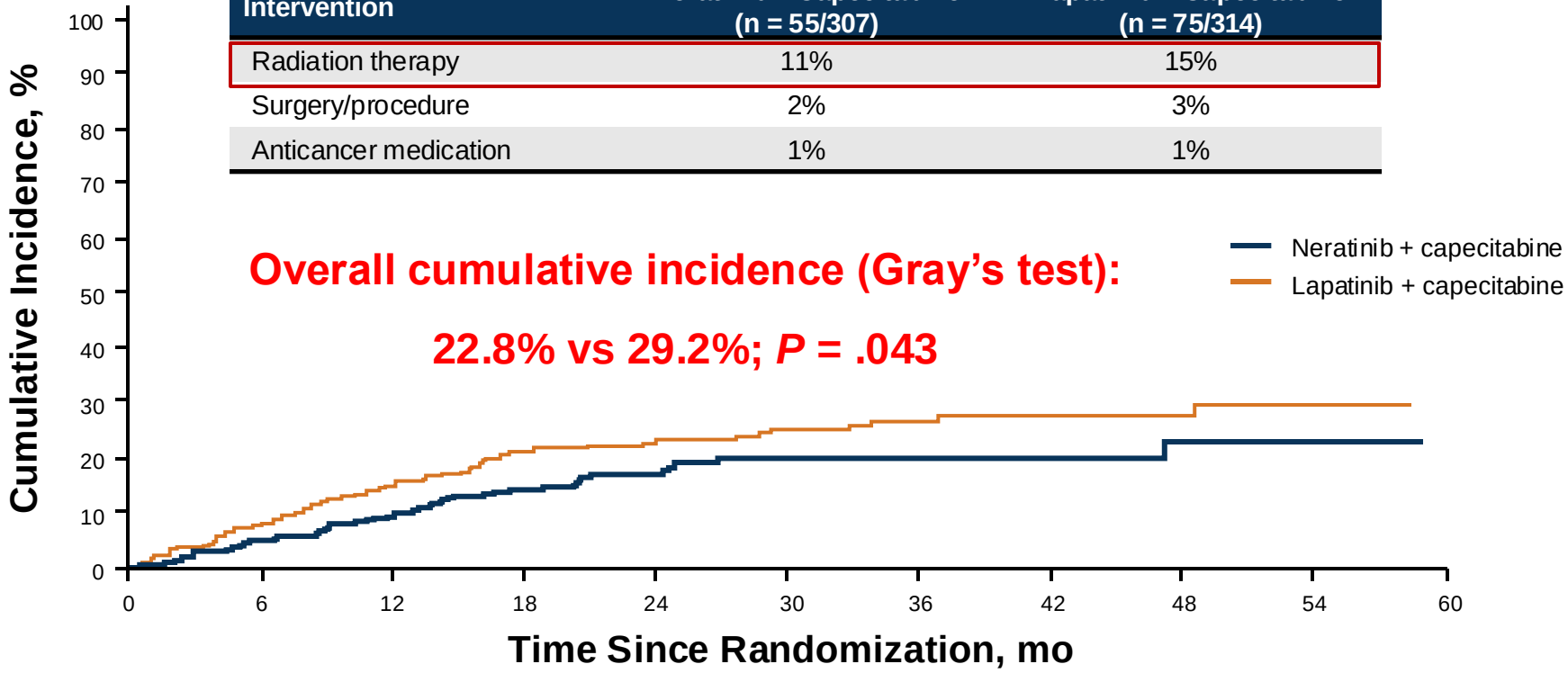
24 vs 22.2mo
Δ1.8 mo
p=ns



Presented by Brufsky et al. 2019 ASCO

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%

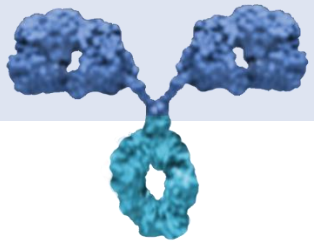


Saura C, et al. J Clin Oncol. 2020 Sep 20;38(27):3138-3149

Margetuximab: Fc engineering Alters Fc Receptor Affinities

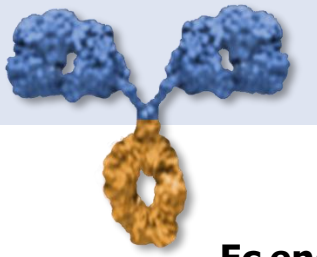
Trastuzumab

Fab:
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival



Fc:
- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

Margetuximab[1,2]



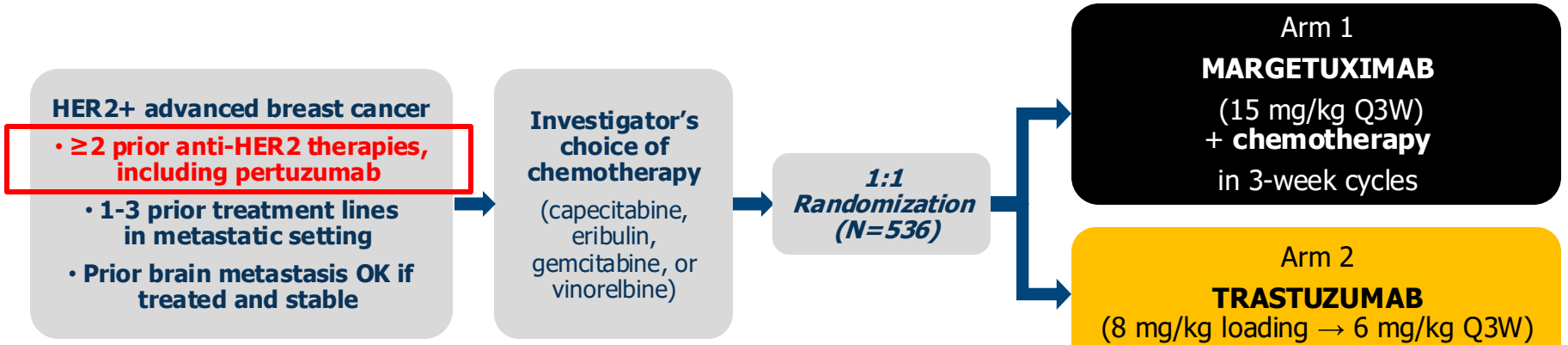
Fab:
- Same specificity and affinity
- Similarly disrupts signaling

Fc engineering:
- ↑ Affinity for activating Fcγ RIIIA (**CD16A**)
- ↓ Affinity for inhibitory Fcγ RIIB (**CD32B**)

1. Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123. 2. Stavenhagen JB, et al. *Cancer Res*. 2007;67(18):8882-8890.

Rugo H, et al. SABCS 2019. Abstract GS1-02.

SOPHIA Study: Randomized Phase 3 Design



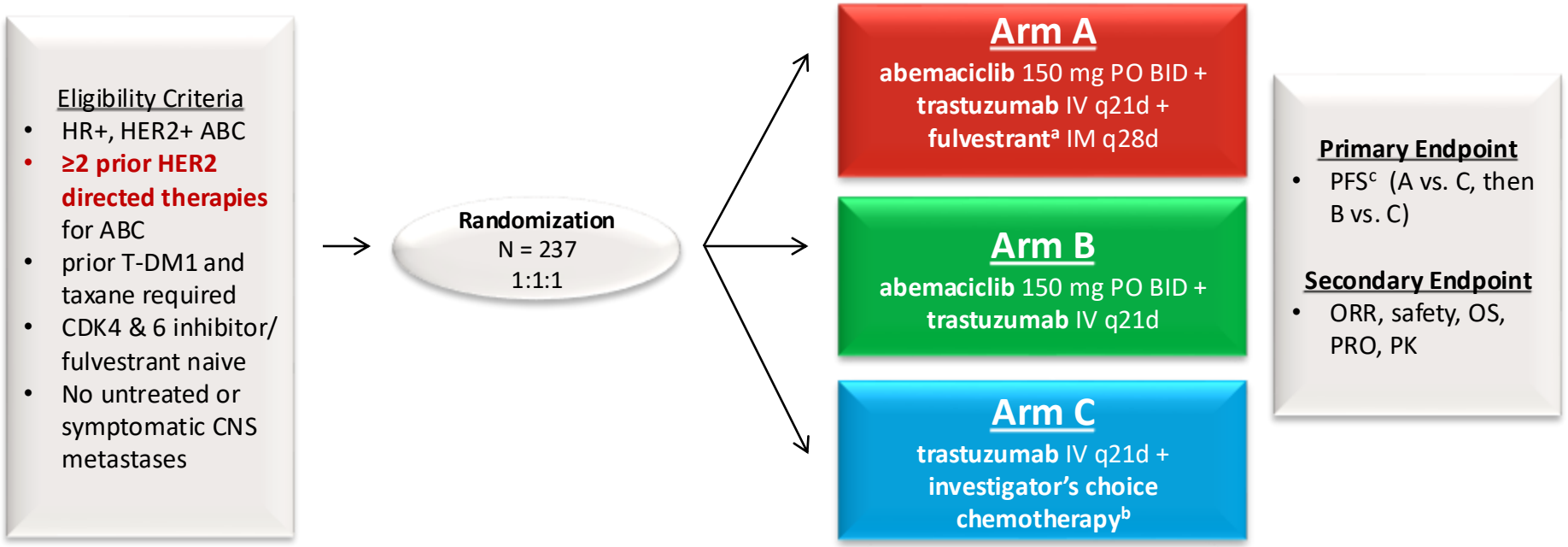
Sequential Primary Endpoints	• **PFS** (by CBA; n=257; HR=0.67; α=0.05; power=90%) • **OS** (n=385; HR=0.75; α=0.05; power=80%)
Secondary Endpoints	• **PFS** (Investigator assessed) • Objective response rate (ORR) by CBA
Tertiary/Exploratory Endpoints	• **ORR** (Investigator assessed) • **Clinical benefit rate** (CBR), **duration of response** (DoR) • **Safety** profile, antidrug antibody • **Effect of CD16A**, CD32A, and CD32B on margetuximab efficacy

Prior Therapy
66-67% ≤ 2 lines
100% Trastuzumab
100% Pertuzumab
91-92% TDM1

Rugo, H et al, SABC 2019

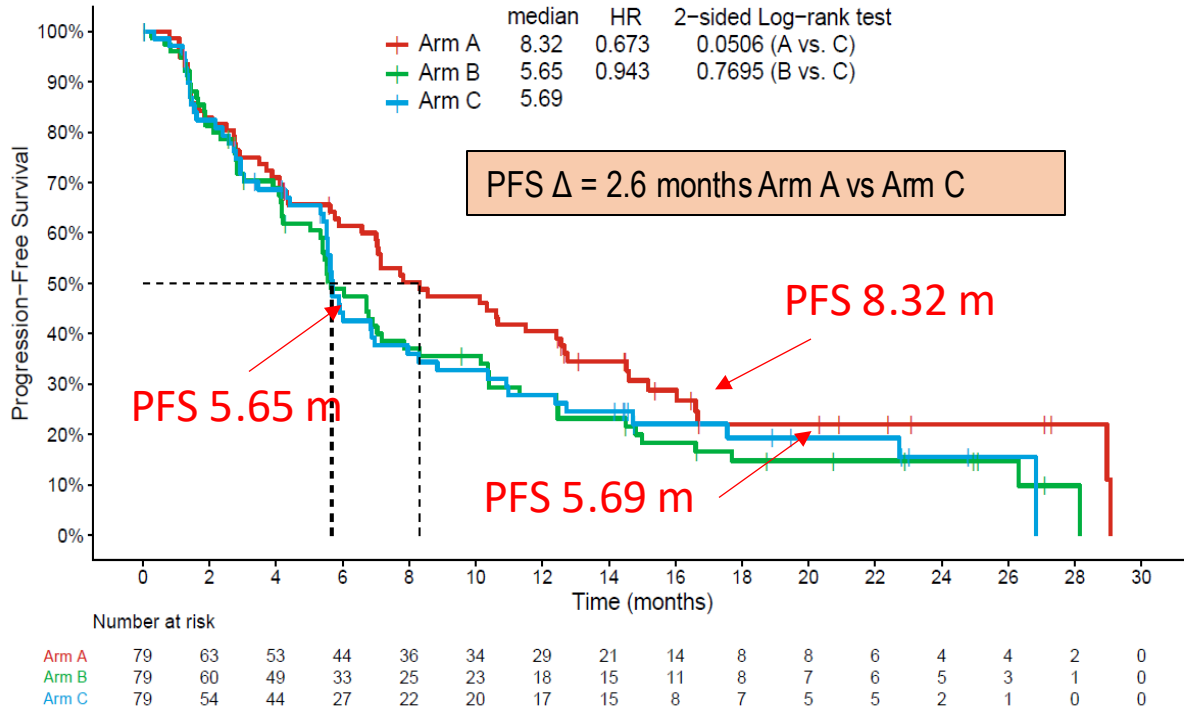
CDK4/6 Inhibition in ER+ HER2+ MBC: monarcHER Trial

Randomized Phase 2



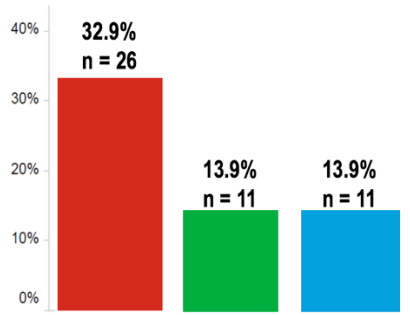
Tolaney et al, ESMO 2019:
Tolaney et al, Lancet Oncol 2020

MONARCHER Trial: PFS and ORR



Arm A= abemaciclib + trastuzumab + fulvestrant; Arm B= abemaciclib + trastuzumab ; Arm C= trastuzumab + chemotherapy

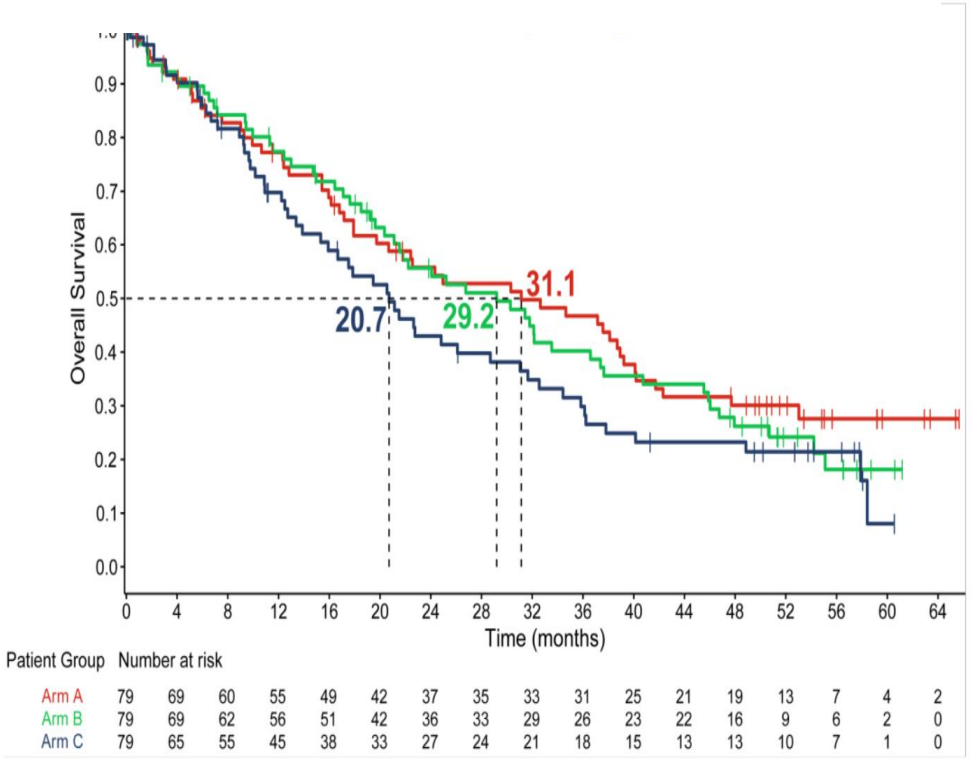
ORR in ITT Population



ITT Population Total N = 237	Arm A N=79	Arm B N=79	Arm C N=79
95% CI (%)	(22.5-43.3)	(6.3-21.6)	(6.3-21.6)
Stratified 2-sided p-value (vs Arm C)	0.0042	1.0000	-
Duration of Response, months	12.5	9.5	not reached

Tolaney et al, ESMO 2019:
Tolaney et al, Lancet oncol 2020

monarcHER Trial: Overall Survival



	Arm A	Arm B	Arm C
Events	50	54	53
mOS, (mo)	31.1	29.2	20.7
HR (95% CI)	0.71 (0.48, 1.05)	0.84 (0.57, 1.23)	N/A
2-sided *P* value	0.086 A vs. C	0.365 B vs. C	
Pre-planned Final OS Analysis Data cutoff: 31 Mar 2022			

Abemaciclib + trastuzumab +/- fulvestrant resulted in numerical improvement in median OS as compared to chemotherapy + trastuzumab.

Andre F et al , ESMO 2022

Future Directions

Novel Treatments for HER2+ MBC In Development

Antibodies/Bispecifics

- Zenocotuzumab
- Zanidatamab
- PRS-343
- BDC-1001
- Runimotamab
- MT-5111
- SBT6050
- SAR-443216
- NJH395
- KNO26

Tyrosine Kinase Inhibitors

- Poziotinib
- Pyrotinib
- Epertinib
- BDTX-189
- DZD1516

ADCs & novel Conjugates

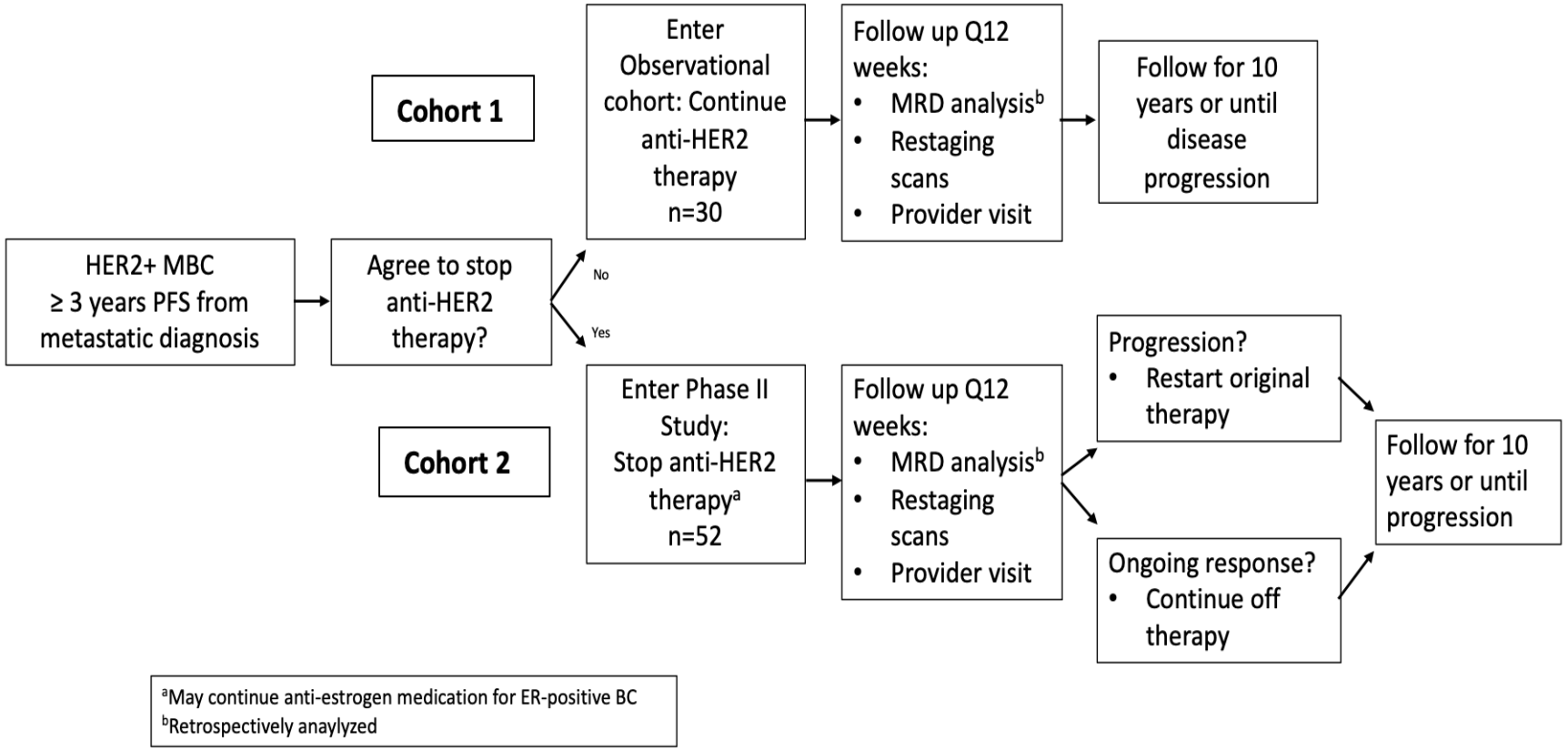
- ARX88
- Zanidatamab Zovodotin
- A166
- ALT-P7
- Disitamab vedotin
- XMT-1522
- ALT-P7
- DB-1303
- FS-1502
- DX 126-262

Immune Therapies/Cellular Therapies

- Vaccines
- CAR-M; CAR-NK

Swain S et al,
Nature Rev 2023

TBCRC Proposal: STOP-HER2 Trial Design



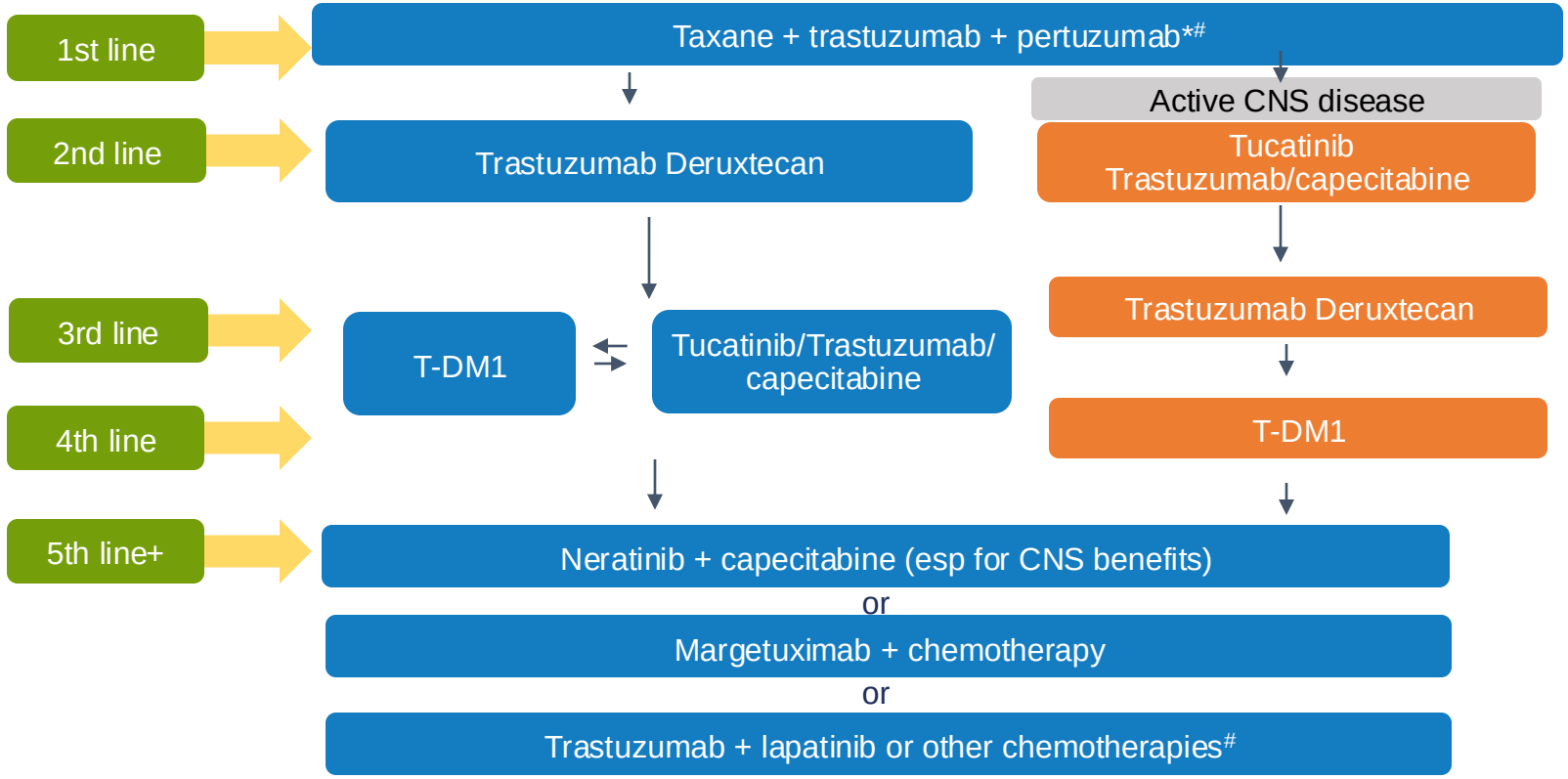
Primary Endpoint: 1- year PFS in Cohort 2

PI: Heather Parsons, DFCI

Summary: HER2+ BC and Beyond

- Anti-HER2 Rxs-revolutionized outcomes for pts with HER2+ MBC
- Novel agents
    - ↑PFS ↑OS
    - Changed the natural history
    - Hold promise for CNS treatment for HER2+BC BM
- Personalizing HER2 Rxs requires understanding
    - Mechanisms of resistance
    - Optimal sequencing of Rxs

A 2024 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

Thank You!