Advanced HER2 positive breast cancer

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Fundación Contigo Contra el Cáncer de la Mujer
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DECLARATION OF INTERESTS

Consulting/Advisor: Roche , AstraZeneca, Seattle Genetics, Daiichi Sankyo, Lilly, Merck Sharp&Dohme, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, Expres2ion Biotechnologies, Jazz Pharmaceuticals, Abbvie, Bridgebio, Biontech, Biocon.

Honoraria: Roche, Novartis, Eisai, Pfizer, Lilly, Merck Sharp&Dohme, Daiichi Sankyo, Astrazeneca, Gilead, Steamline Therapeutics.

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Stock: MAJ3 Capital, Leuko (relative)

Travel, accommodation, expenses: Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, Astrazeneca, Gilead, Merck Sharp&Dhome, Steamline Therapeutics.

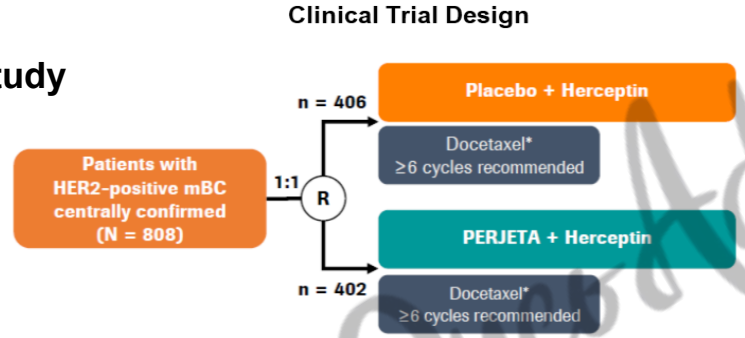
Patents:

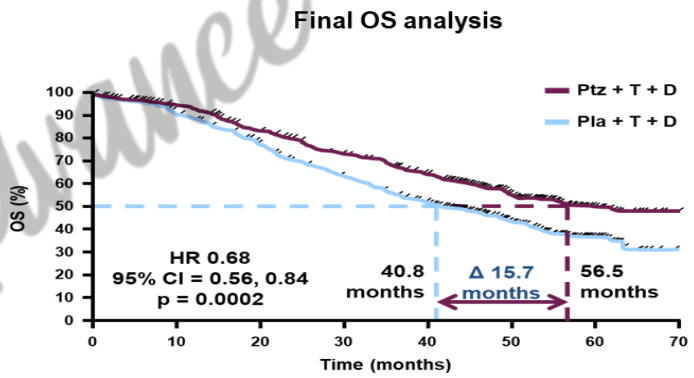
Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. ISSUED

Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/ 0338368 A1. LICENSED

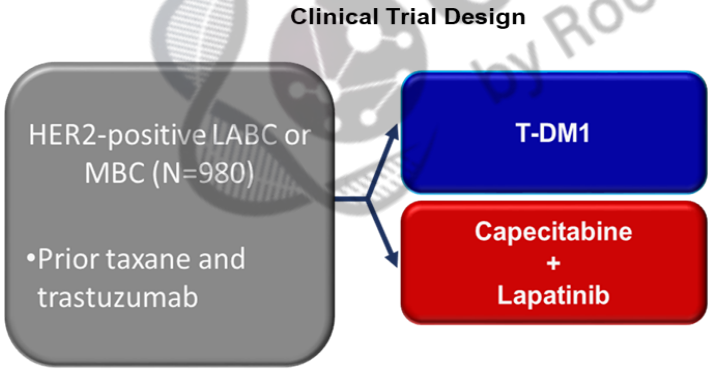
“Up to 2022” first- and second-line preferred strategies

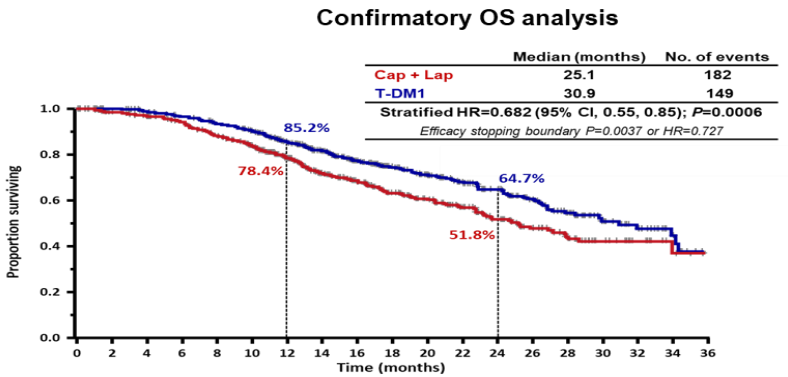
CLEOPATRA Study





EMILIA Study

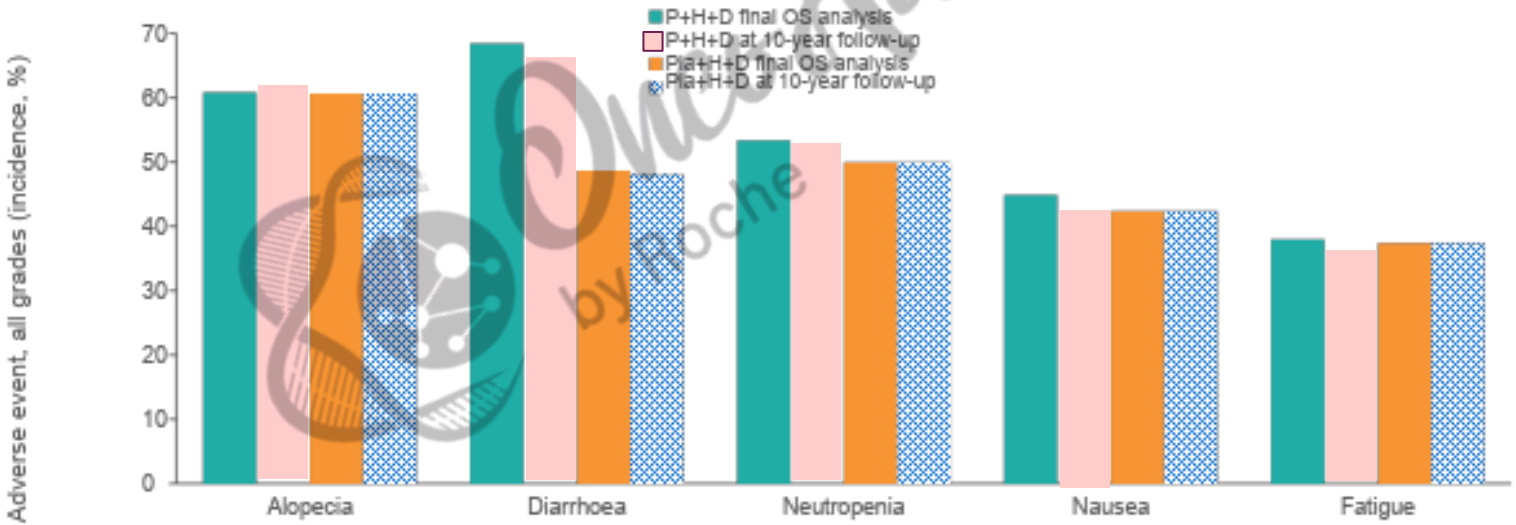




Baselga J, et al. NEJM 2012; Swain S, et al. NEJM 2015; Verma S, et al. NEJM 2012

CLEOPATRA: Safety profile of PH was maintained at 10-year follow-up[1,2]

- At 10-year follow-up, there was a higher incidence of diarrhoea and rash with Pertuzumab compared with placebo, both at any grade and at grade ≥3[1]
- Neutropenia was the most common grade 3–4 AE (Pertuzumab 49% [200/408], placebo 46% [183/396])[1]



AE,, adverse event, D, docetaxel; H, Trastuzumab; P, Pertuzumab; Pla, placebo.

1. Swain SM, *et al. Lancet Oncol* 2020; **21**:519–530; 2. Swain SM, *et al. N Engl J Med* 2015; **372**:724–734 (suppl. appendix).

Phila Study

Key eligibility criteria
- Pathologically confirmed HER2-positive metastatic breast cancer
- Treatment-naive
- Measurable disease (RECIST v1.1)
- ECOG performance status of 0 or 1

R 1:1

Pyrotinib + HT group
Pyrotinib (400 mg, orally, qd) + Trastuzumab (8 mg/kg in cycle 1 and 6 mg/kg in subsequent cycles, IV) + Docetaxel (75 mg/m², IV) on day 1 of each 21-day cycle

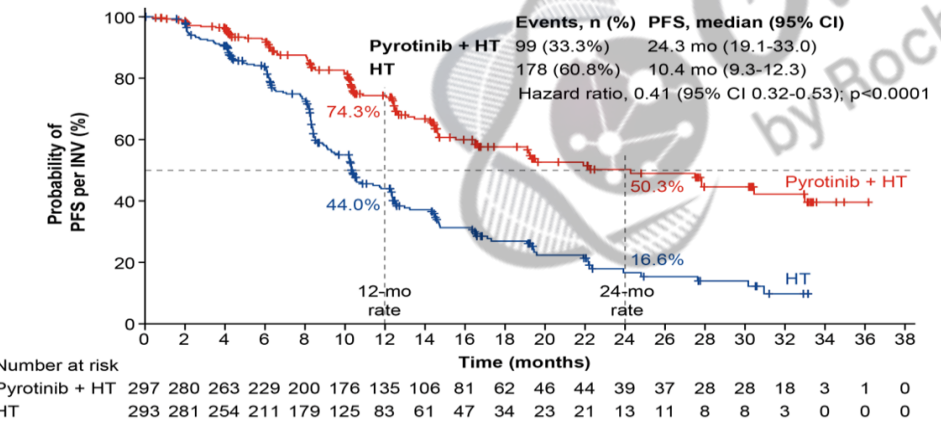
Stratification factors:
- ✓ Prior neoadjuvant or adjuvant trastuzumab (yes vs no)
- ✓ Hormone receptor status (ER- and/or PR-positive vs ER- and PR-negative)

HT group
Placebo + Trastuzumab (8 mg/kg in cycle 1 and 6 mg/kg in subsequent cycles, IV) + Docetaxel (75 mg/m², IV) on day 1 of each 21-day cycle

Primary endpoint:
- PFS (per INV)

Secondary endpoints:
- PFS (per IRC)
- OS
- ORR
- DoR
- CBR
- Safety

PFS (per INV)



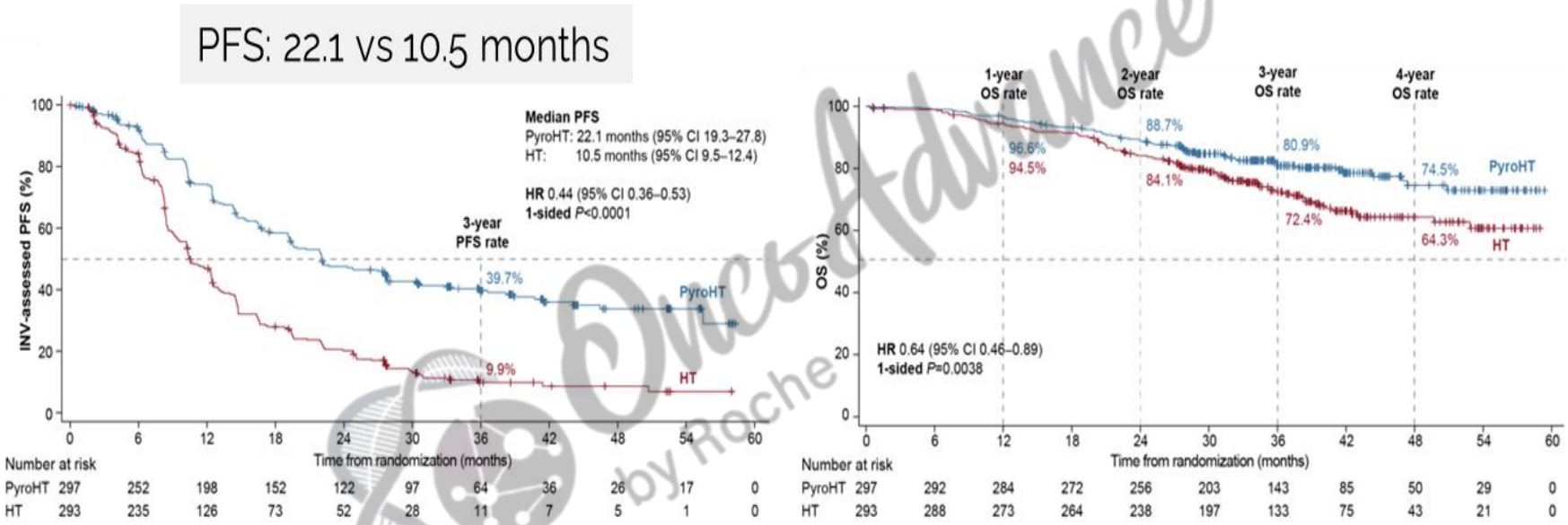
ORR

	Per INV		Per IRC	
	Pyrotinib + HT (n=297)	HT (n=293)	Pyrotinib + HT (n=297)	HT (n=293)
Best overall response				
Complete response	19 (6.4)	8 (2.7)	13 (4.4)	6 (2.0)
Partial response	227 (76.4)	199 (67.9)	249 (83.8)	207 (70.6)
Stable disease	31 (10.4)	63 (21.5)	15 (5.1)	54 (18.4)
Progressive disease	8 (2.7)	16 (5.5)	7 (2.4)	18 (6.1)
Not assessable	12 (4.0)	7 (2.4)	13 (4.4)	8 (2.7)
ORR	246 (82.8%, 78.1-86.9)	207 (70.6%, 65.1-75.8)	262 (88.2%, 84.0-91.7)	213 (72.7%, 67.2-77.7)
DoR, months	25.9 (17.3-NR)	9.5 (8.3-10.6)	NR (20.0-NR)	10.3 (8.3-12.3)

Data are n (%), n (%, 95% CI), or median (95% CI).

Xu B, et al. ESMO 2022

Phila Study (updated data SABCS 2024)



- **Grade ≥3 diarrhea: 47.8% vs 4.4%**

- **% of pts who received subsequent anti-HER2**
  Pyrotinib arm: 52%
  HT arm: 76%

Xu B, et al. SABCS 2024

New TKIs

Clinical Trial Designs

HER2CLIMB[1]

Key Eligibility Criteria

- Measurable or non-measurable HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG 0, 1
- Brain MRI at baseline
  - No evidence of brain metastases, or
  - Untreated, previously treated stable, or previously treated progressing, brain metastases not needing immediate local therapy

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
Treatment (21-day cycle)

Tucatinib 300 mg PO BID +
Trastuzumab 6 mg/Kg Q3W (loading dose 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

Placebo + Trastuzumab + Capecitabine
Treatment (21-day cycle)

Placebo (Pbo) +
Trastuzumab 6 mg/Kg Q3W (loading dose 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

NALA Study[2]

HER2+ MBC (N=621)

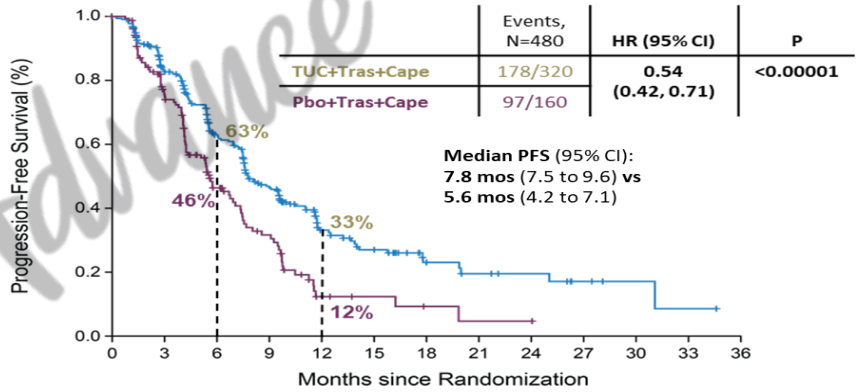
•Prior treatment with at least two HER2-directed regimens for metastatic breast cancer

1:1

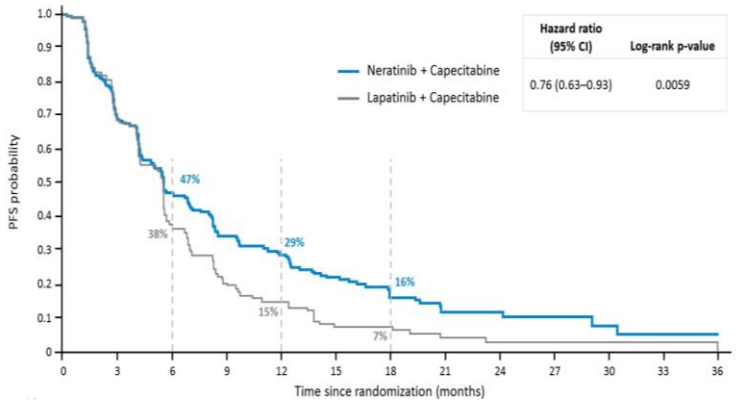
Capecitabine + Neratinib

Capecitabine + Lapatinib

Positive PFS data



	Events, N=480	HR (95% CI)	P
TUC+Tras+Cape	178/320	0.54 (0.42, 0.71)	<0.00001
Pbo+Tras+Cape	97/160		



Hazard ratio (95% CI)	Log-rank p-value
0.76 (0.63–0.93)	0.0059

1. Murthy R, et al. NEJM 2020; 2. Brufsky A, et al. ASCO 2019;

New TKIs

Clinical Trial Designs

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N=202

Placebo + Trastuzumab + Capecitabine
Treatment (21-day cycle)

Placebo (Pbo) +
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NALA Study[2]

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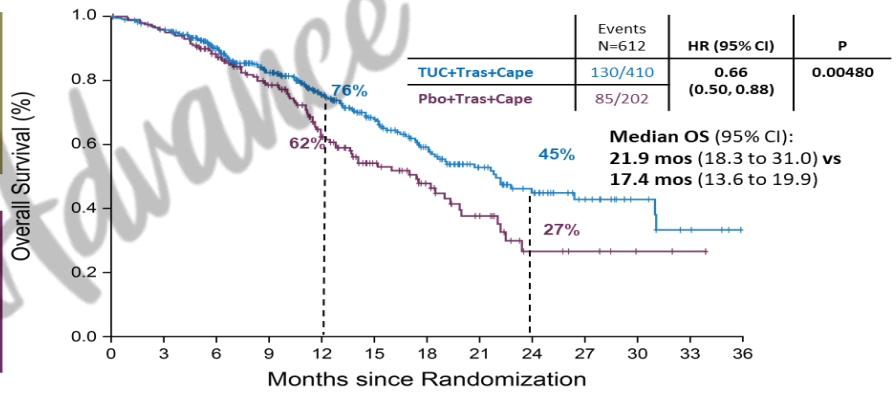
•Prior treatment with at least two HER2-directed regimens for metastatic breast cancer

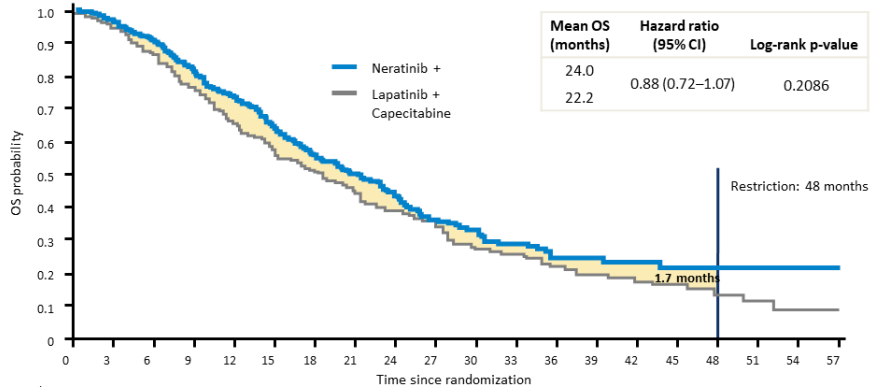
1:1

- Capecitabine + Neratinib
- Capecitabine + Lapatinib

OS data



	Events N=612	HR (95% CI)	P
TUC+Tras+Cape	130/410	0.66 (0.50, 0.88)	0.00480
Pbo+Tras+Cape	85/202		



Mean OS (months)	Hazard ratio (95% CI)	Log-rank p-value
24.0 22.2	0.88 (0.72–1.07)	0.2086

1. Murthy R, et al. NEJM 2020; 2. Brufsky A, et al. ASCO 2019;

New TKIs

Clinical Trial Designs

HERCLIMB[1]

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Tucatinib + Trastuzumab + Capecitabine
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N=202

Placebo + Trastuzumab + Capecitabine
Treatment (21-day cycle)

Placebo (Pbo) +
Trastuzumab 6 mg/Kg Q3W (loading dose 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

NALA Study[2]

HER2+ MBC (N=621)

•Prior treatment with at least two HER2-directed regimens for metastatic breast cancer

1:1

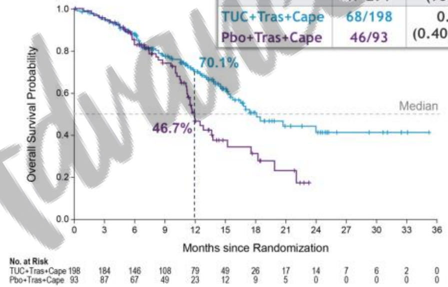
Capecitabine + Neratinib

Capecitabine + Lapatinib

Special considerations

OS data in pts with brain mets

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	0.005
Pbo+Tras+Cape	46/93		



Risk of death was reduced by 42% in patients with brain metastases

One-year OS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
70.1% (62.1, 76.7)	46.7% (33.9, 58.4)
Median OS (95% CI):	
18.1 months (15.5, NE)	12.0 months (11.2, 15.2)

NE: not estimable

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.

Most frequent TEAEs

Safety Outcome	Neratinib + Capecitabine (n = 303)		Lapatinib + Capecitabine (n = 311)	
	All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %
Any TEAE	100	61	99	60
Diarrhea	83	24	66	13
Hand-foot syndrome	46	10	56	11
Hypokalemia	12	5	14	6
Nausea	53	4	42	3
Vomiting	46	4	31	2
Fatigue	34	3	31	3
Neutropenia	7	3	5	2
Asthenia	12	3	12	2
Decreased appetite	35	3	22	2
Dehydration	6	2	6	2

Treatment Discontinuations due to TEAE: N+C= 10.9 % vs L+ C= 14.5%

1. Murthy R, et al. NEJM 2020; 2. Brufsky A, et al. ASCO 2019;

HER2CLIMB-02: TDM1 + Tucatinib/Placebo

- 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

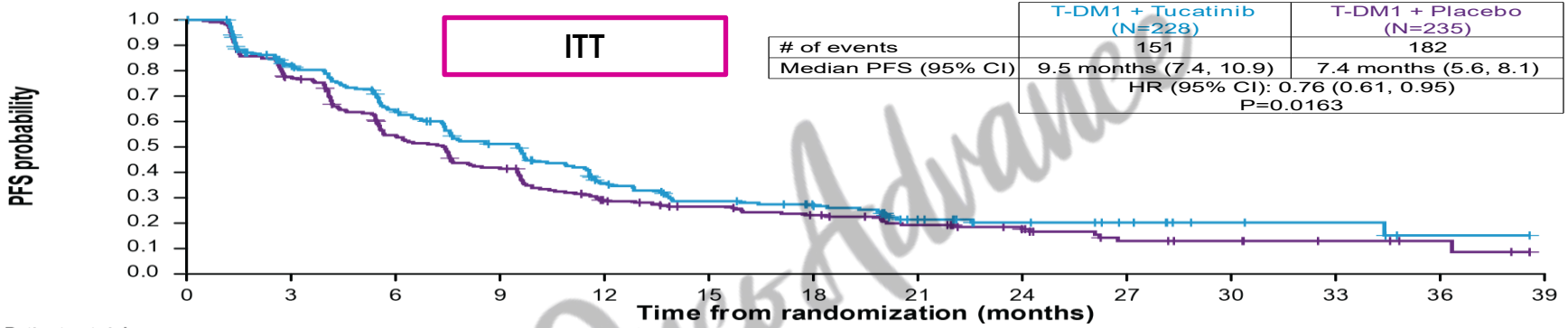
Key Secondary (hierarchical)
- OS
- PFS in patients with brain metastases
- cORR per RECIST v1.1
- OS in patients with brain metastases

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]

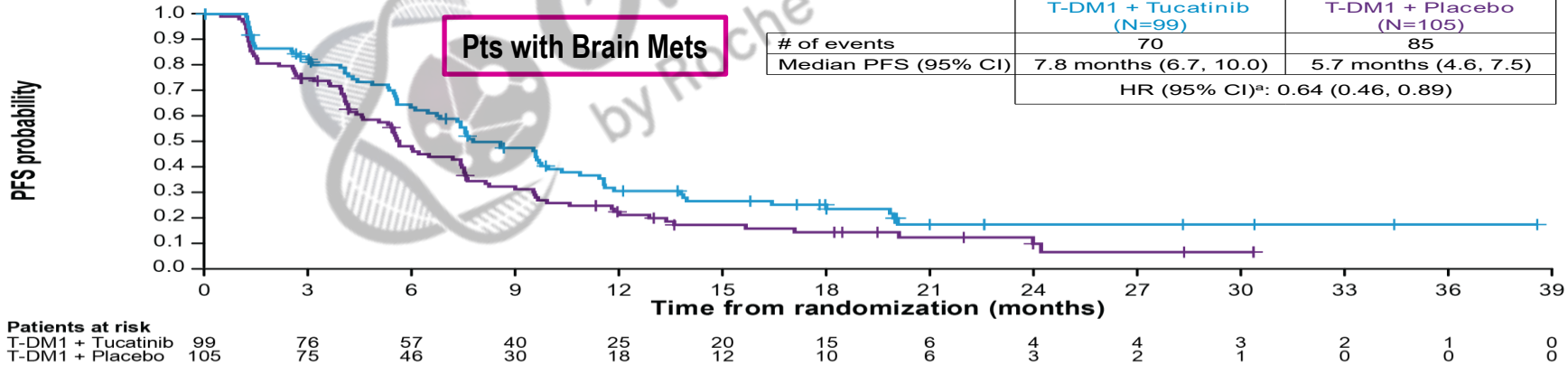
	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
Median prior lines of systemic therapy in metastatic setting (range)	1 (0-8)	1 (0-6)
Prior lines of systemic therapy in metastatic setting, n (%)		
0	29 (12.7)	33 (14.0)
1	146 (64.0)	150 (63.8)
2	36 (15.8)	31 (13.2)
≥3	17 (7.5)	21 (8.9)
Received prior pertuzumab treatment, n (%)	202 (88.6)	214 (91.1)
Received prior anti-HER2 TKIs, n (%)	3 (1.3)	5 (2.1)

Hurvitz S, et al. SABCS 2023

HER2CLIMB-02: TDM1 + Tucatinib/Placebo



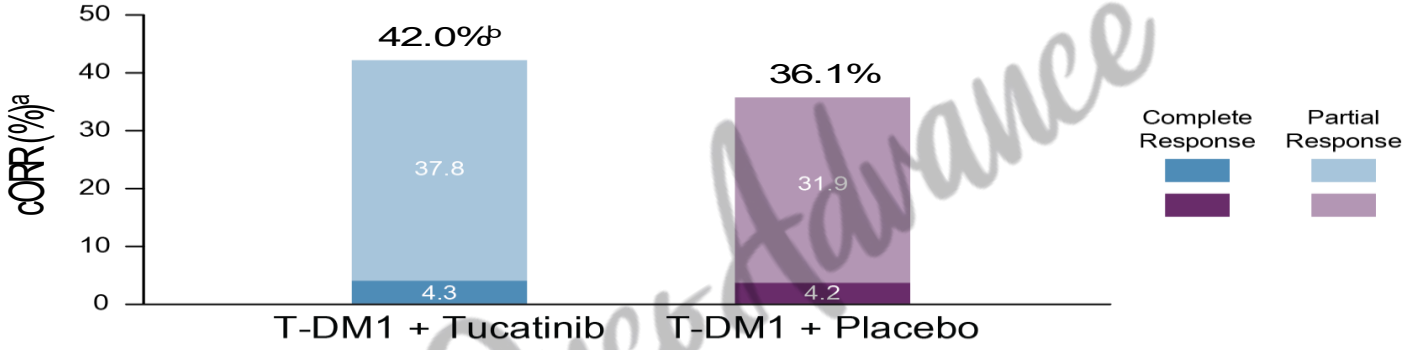
	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	151	182
Median PFS (95% CI)	9.5 months (7.4, 10.9)	7.4 months (5.6, 8.1)
	HR (95% CI): 0.76 (0.61, 0.95) P=0.0163	

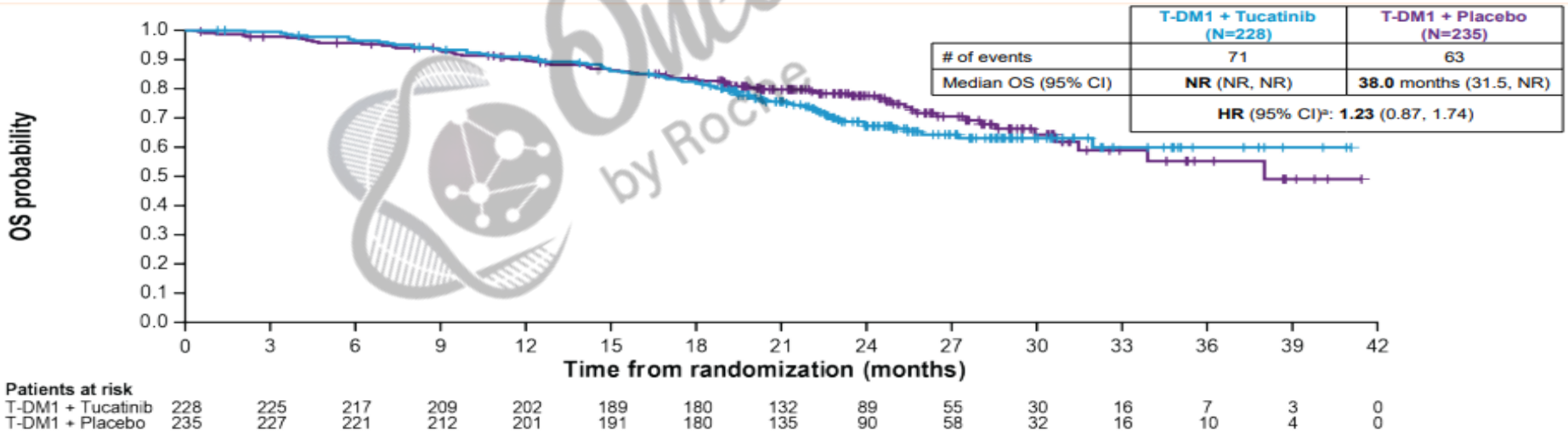


	T-DM1 + Tucatinib (N=99)	T-DM1 + Placebo (N=105)
# of events	70	85
Median PFS (95% CI)	7.8 months (6.7, 10.0)	5.7 months (4.6, 7.5)
	HR (95% CI)[a]: 0.64 (0.46, 0.89)	

Hurvitz S, et al. SABCS 2023

HER2CLIMB-02: TDM1 + Tucatinib/Placebo



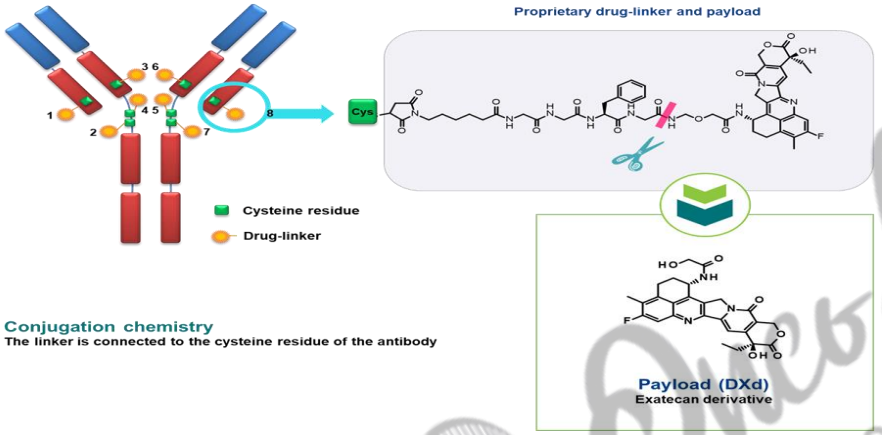


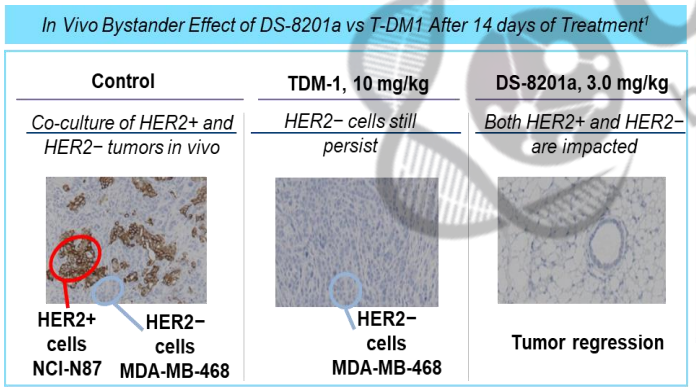
	T-DM1 + Tucatinib (N=228)	T-DM1 + Placebo (N=235)
# of events	71	63
Median OS (95% CI)	**NR** (NR, NR)	**38.0** months (31.5, NR)
	HR (95% CI)[a]: **1.23** (0.87, 1.74)	

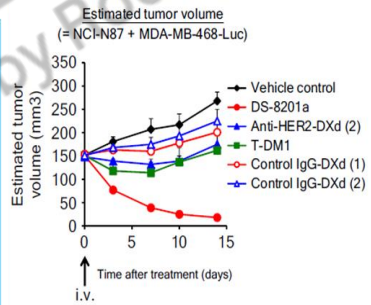
Hurvitz S, et al. SABCS 2023

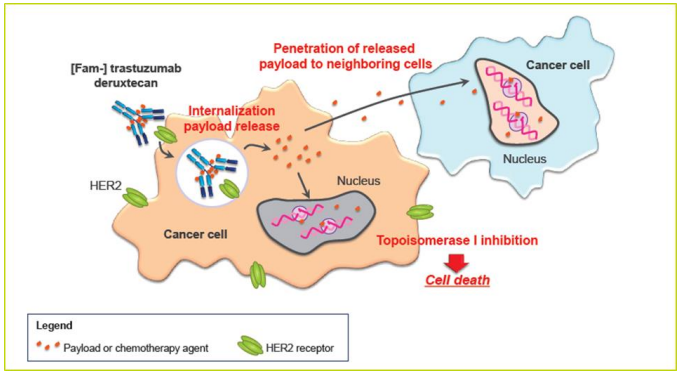
Trastuzumab-Deruxtecan

- Payload with a different mechanism of action
- High potency of payload
- Payload with short systemic half-life
- Bystander effect
- Stable linker-payload
- Tumor-selective cleavable linker
- High drug-to-antibody ratio (~1:8)







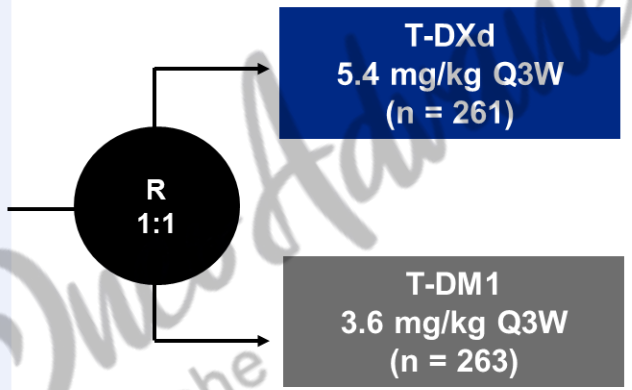


Iwata, et al. ASCO 2018; Ogitani, et al. Cancer Science 2016

Trastuzumab-Deruxtecan: DB03 Phase III study

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

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Ph3, phase 3; Q3W, every 3 weeks.
[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; Cortes J, et al. NEJM 2022

Trastuzumab Deruxtecan in "second-line" Destiny-Breast 03 study: UPDATED at SABCS

Clinical Trial Design (DB03)

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

R 1:1

- T-DXd 5.4 mg/kg Q3W (n = 261)
- T-DM1 3.6 mg/kg Q3W (n = 263)

Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

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

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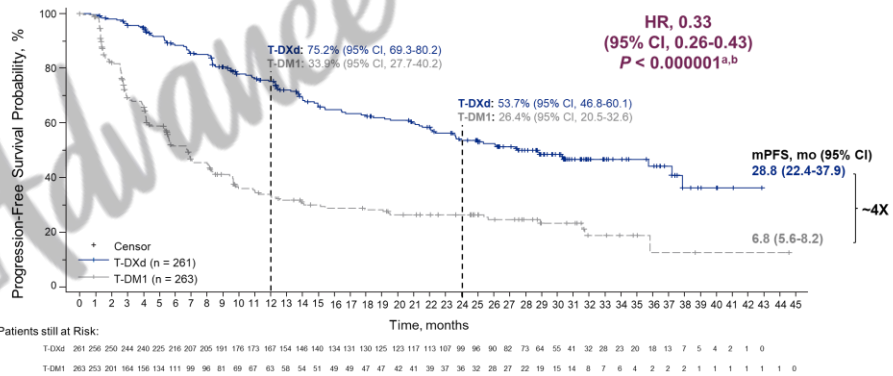
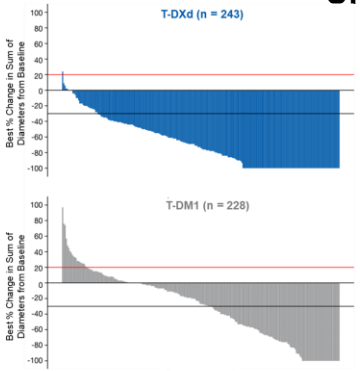
PFS



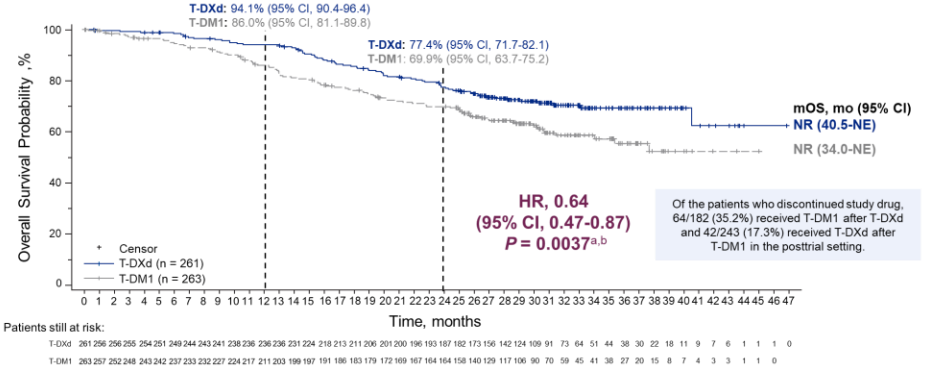
ORR



	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal *P* value	< 0.0001	
CR, n (%)	55 (**21.1**)	25 (**9.5**)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)
CBR, n (%) [95% CI]	233 (89.3) [84.9-92.8]	122 (46.4) [40.2-52.6]
Nominal *P* value	< 0.0001	
mDoR by BICR, months (95% CI)	**36.6** (22.4-NE)	**23.8** (12.6-34.7)

BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; mDoR, median duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Red line at 20% indicates progressive disease; black line at −30% indicates partial response.
[a]Only patients with measurable disease at baseline and at least 1 postbaseline target lesion assessment were included.

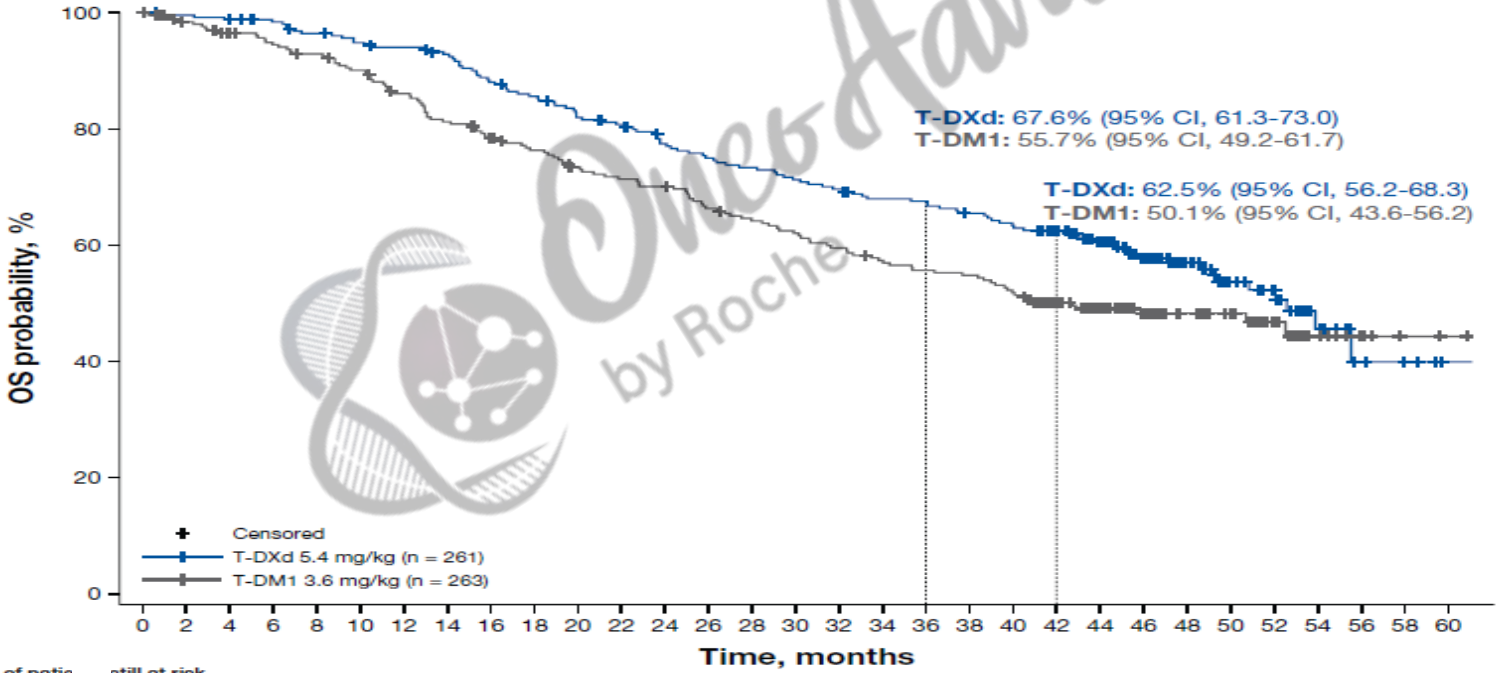
OS



Hurvitz S, et al. SABCS 2022; Lancet 2022

DB03 Phase III study: Updated OS

	T-DXd n = 261	T-DM1 n = 263
Median (95% CI), months	52.6 (48.7-NE)	42.7 (35.4-NE)
HR (95% CI)	0.73 (0.56-0.94)	
Patients with events, n (%)	110 (42.1)	126 (47.9)



Hamilton E, et al. ASCO 2024; Cortes J, et al Nat Med 2024

DB03 Phase III study: Toxicity

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[f]	93 (36.2)	1 (0.4)	6 (2.3)	0

Most drug-related TEAEs were gastrointestinal or hematological in nature

Cortes J, et al. ESMO 2021; Cortes J, et al. NEJM 2022

Updated Adverse Events of Special Interest: ILD

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- Adjudicated drug-related ILD/pneumonitis rates were similar to other mBC trials with T-DXd[1,2]
- With longer treatment exposure and follow-up, the ILD/pneumonitis rate increased from 10.5% in the PFS interim analysis[3] to 15.2%
  - There were 4 additional grade 1, 8 additional grade 2, and no additional grade 3 events
- The overall incidence of grade 3 events (0.8%) was the same as in the PFS interim analysis[3]
- There were no adjudicated drug-related grade 4 or 5 events

Hurvitz S, et al. SABCS 2022; Hurvitz S, et al. Lancet 2022

DB02: randomized phase 3 study

Clinical Trial Design (DB02)

Key eligibility criteria[a]
- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 406)

TPC
Per label (n = 202)
- Trastuzumab / Capecitabine
or
- Lapatinib / Capecitabine

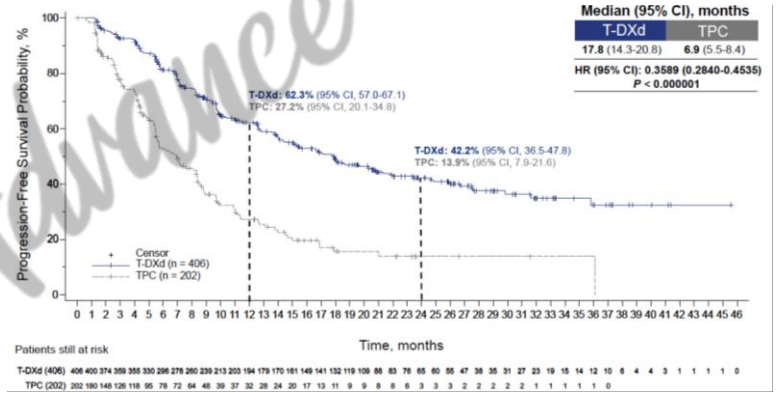
Primary endpoint
- PFS (BICR[b])

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR[b])
- DoR (BICR[b])
- PFS (investigator)
- Safety

Exploratory endpoints
- CBR (BICR[b])
- PFS2[c] (investigator)

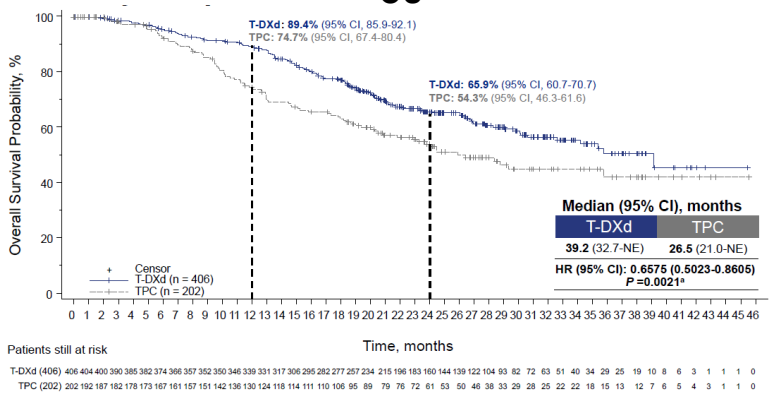
PFS



ORR

	T-DXd n = 406	TPC n = 202
Confirmed ORR by BICR,[a] n (%) [95% CI]	**283 (69.7) [65.0-74.1]**	**59 (29.2) [23.0-36.0]**
	$P < 0.0001$[b]	
Confirmed best overall response, n (%)		
CR	57 (14.0)	10 (5.0)
PR	226 (55.7)	49 (24.3)
SD	95 (23.4)	94 (46.5)
PD	19 (4.7)	26 (12.9)
Not evaluable	9 (2.2)	23 (11.4)
mDoR by BICR,[c] months (95% CI)	19.6 (15.9-NE)	8.3 (5.8-9.5)
CBR by BICR,[d] % (95% CI)	82.3 (78.2-85.9)	46.0 (39.0-53.2)
mPFS by investigator,[e] months (95% CI)	16.7 (14.3-19.6)	5.5 (4.4-7.0)
mPFS2,[e] months (95% CI)	35.8 (28.4-NE)	15.8 (13.5-21.0)

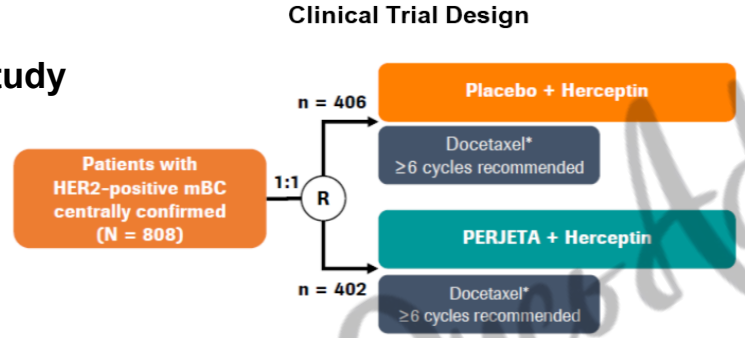
OS

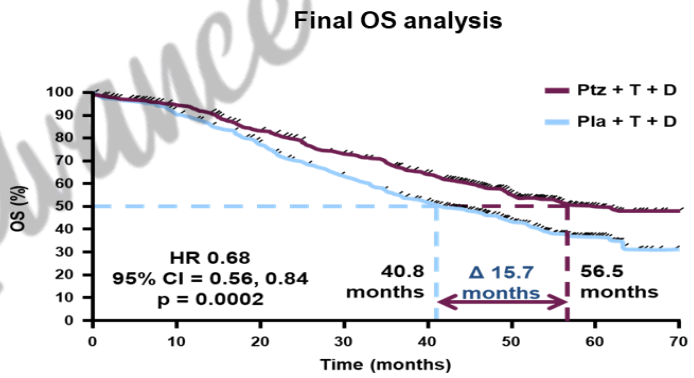


Krop I, et al. SABCS 2022

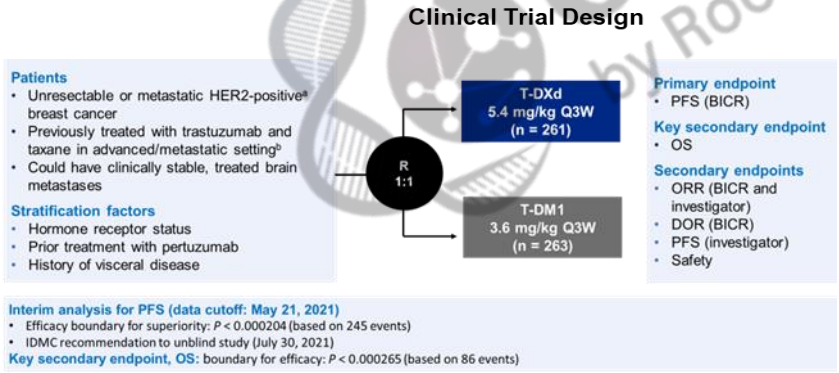
“Up to 2026?” first- and second-line preferred strategies

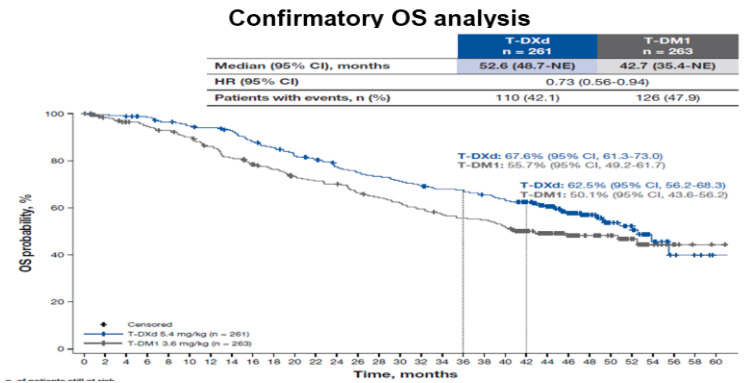
CLEOPATRA Study





DB03 Study





Baselga J, et al. NEJM 2012; Swain S, et al. NEJM 2015; Cortes Nat Med 2024

Can we optimize the Cleopatra strategy?

Can we optimize the Cleopatra strategy?
AFT-38 PATINA Study Design

Registration

- Histologically confirmed HR+,HER2+ mBC
- No prior treatment in the advanced setting beyond induction treatment
- 6-8 cycles of treatment, including trastuzumab ± pertuzumab and taxane/vinorelbine

Key eligibility criteria

- Completion of induction chemotherapy and no evidence of disease progression (i.e., CR, PR, or SD)

N=518

R 1:1

- **Palbociclib (125 mg PO QD D1-D21) Trastuzumab ± pertuzumab + endocrine therapy***
- **Trastuzumab ± pertuzumab + endocrine therapy***

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors

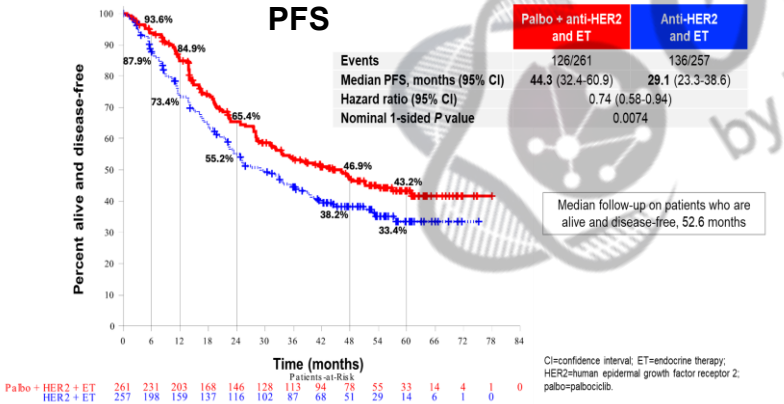
- Pertuzumab use (yes vs no)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs no, including de novo)†
- Response to induction therapy (CR or PR vs SD) by investigator assessment†
- Type of endocrine therapy (fulvestrant vs aromatase inhibitor)

Metzger O, et al. SABCS 2024

PATINA Study: Baseline Characteristics and outcomes

	Palbociclib + anti-HER2 and ET (N=261)	Anti-HER2 therapy and ET (N=257)	Total (N=518)
Pertuzumab use, n (%)			
No	8 (3.1)	6 (2.3)	14 (2.7)
Yes	253 (96.9)	251 (97.7)	504 (97.3)
Type of endocrine therapy, n (%)			
Aromatase inhibitor	237 (90.8)	234 (91.1)	471 (90.9)
Fulvestrant	24 (9.2)	23 (8.9)	47 (9.1)
Prior anti-HER2 therapy in the (neo)adjuvant setting,* n (%)			
No	71 (27.2)	75 (29.2)	146 (28.2)
Yes	190 (72.8)	182 (70.8)	372 (71.8)
Best response to induction therapy by investigator assessment,* n (%)			
CR or PR	179 (68.6)	176 (68.5)	355 (68.5)
SD	82 (31.4)	81 (31.5)	163 (31.5)

PFS

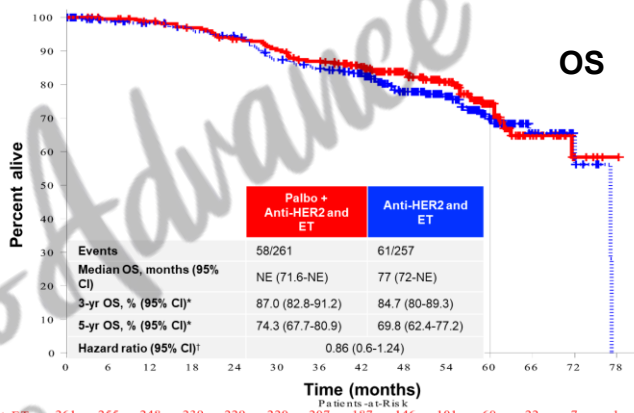


	Palbo + anti-HER2 and ET	Anti-HER2 and ET
Events	126/261	136/257
Median PFS, months (95% CI)	**44.3** (32.4-60.9)	**29.1** (23.3-38.6)
Hazard ratio (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided *P* value	0.0074	

Median follow-up on patients who are alive and disease-free, 52.6 months

CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; palbo=palbociclib.

OS



	Palbo + Anti-HER2 and ET	Anti-HER2 and ET
Events	58/261	61/257
Median OS, months (95% CI)	NE (71.6-NE)	77 (72-NE)
3-yr OS, % (95% CI)*	87.0 (82.8-91.2)	84.7 (80-89.3)
5-yr OS, % (95% CI)*	74.3 (67.7-80.9)	69.8 (62.4-77.2)
Hazard ratio (95% CI)†	0.86 (0.6-1.24)	

*Kaplan-Meier method. †Unstratified Cox model. CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; NE=not evaluable; OS=overall survival; palbo=palbociclib.

Adverse Events, n (%)*	Palbociclib + anti-HER2 and ET (N=261)			Anti-HER2 and ET (N=248)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Neutropenia	52 (19.9)	165 (63.2)	12 (4.6)	10 (4.0)	11 (4.4)	0 (0.0)
White blood cell count decreased	30 (11.5)	30 (11.5)	1 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)
Fatigue	60 (22.9)	14 (5.4)	0 (0.0)	32 (12.9)	0 (0.0)	0 (0.0)
Stomatitis	45 (17.2)	11 (4.2)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)
Diarrhea	69 (26.4)	29 (11.1)	0 (0.0)	26 (10.5)	4 (1.6)	0 (0.0)
Upper respiratory tract infection	30 (11.5)	1 (0.4)	0 (0.0)	16 (6.5)	0 (0.0)	0 (0.0)
Urinary tract infection	26 (10.0)	2 (0.8)	0 (0.0)	19 (7.7)	1 (0.4)	0 (0.0)
Arthralgia	23 (8.8)	4 (1.5)	0 (0.0)	44 (17.7)	3 (1.2)	0 (0.0)
Ejection fraction decreased	22 (8.4)	1 (0.4)	0 (0.0)	21 (8.5)	8 (3.2)	0 (0.0)
Cardiac heart failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)

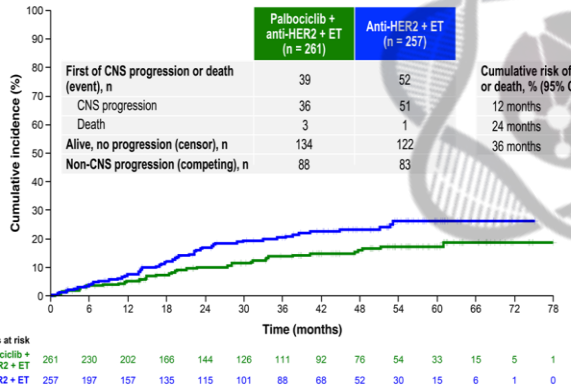
- The incidence of grade ≥4 adverse events regardless of treatment attribution was similar across study arms (12.3% vs 8.9% for palbociclib-containing arm vs control; *P*=0.21)
- Treatment discontinuation due to AEs were reported in 14 (7.5%) of patients in the palbociclib arm
- No treatment-related deaths were reported in either arm of the study

Metzger O, et al. SABCS 2024

PATINA Study: Baseline Characteristics and CNS outcomes

	Palbociclib + anti-HER2 + ET (n = 261)	Anti-HER2 + ET (n = 257)	Total (N = 518)
Baseline site of metastases, n (%)[a,b]			
CNS	11 (4.2)	9 (3.5)	20 (3.9)
Non-visceral	57 (21.8)	60 (23.5)	117 (22.7)
Visceral	193 (73.9)	186 (72.9)	379 (73.4)

Cumulative Incidence of CNS Progression or Death
All Randomized Patients



	Palbociclib + anti-HER2 + ET (n = 261)	Anti-HER2 + ET (n = 257)
First of CNS progression or death (event), n	39	52
CNS progression	36	51
Death	3	1
Alive, no progression (censor), n	134	122
Non-CNS progression (competing), n	88	83

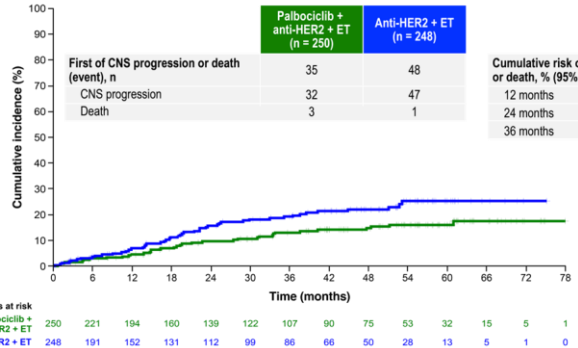
Cumulative risk of CNS progression or death, % (95% CI)	Palbociclib + anti-HER2 + ET (n = 261)	Anti-HER2 + ET (n = 257)
12 months	5.2 (2.9–8.5)	7.5 (4.6–11.5)
24 months	10.1 (6.7–14.3)	17.0 (12.3–22.3)
36 months	13.8 (9.7–18.6)	20.4 (15.3–26.1)

Patients at risk

Palbociclib + anti-HER2 + ET	261	230	202	166	144	126	111	92	76	54	33	15	5	1
Anti-HER2 + ET	257	197	157	135	115	101	88	68	52	30	15	6	1	0

- At 36 months, the cumulative incidence of CNS progression or death was 13.8% vs 20.4% for palbociclib vs control (Gray's test $P = 0.0404$).

Cumulative Incidence of CNS Progression or Death
Patients Without CNS Metastases at Baseline



	Palbociclib + anti-HER2 + ET (n = 250)	Anti-HER2 + ET (n = 248)
First of CNS progression or death (event), n	35	48
CNS progression	32	47
Death	3	1

Cumulative risk of CNS progression or death, % (95% CI)	Palbociclib + anti-HER2 + ET (n = 250)	Anti-HER2 + ET (n = 248)
12 months	4.6 (2.5–7.9)	6.9 (4.0–10.8)
24 months	9.7 (6.3–13.9)	15.7 (11.1–20.9)
36 months	13.0 (9.0–17.9)	19.2 (14.2–24.9)

Patients at risk

Palbociclib + anti-HER2 + ET	250	221	194	160	139	122	107	90	75	53	32	15	5	1
Anti-HER2 + ET	248	191	152	131	112	99	86	66	50	28	13	5	1	0

Among patients without CNS metastases at baseline:

- CNS progression was observed in 12.8% (95% CI, 8.9–17.6) of patients in the palbociclib arm and 19.0% (95% CI, 14.3–24.4) of patients in the control arm.
- The CNS benefit with palbociclib was maintained, with a cumulative risk of CNS progression or death of 13.0% vs 19.2% for palbociclib vs control at 36 months (Gray's test $P = 0.0378$).

Metzger O, et al. SABCS 2025

Can we optimize the Cleopatra strategy?

HER2CLIMB-05 Trial

Clinical Trial Design

Key Eligibility Criteria

- Centrally confirmed HER2+ MBC
- No evidence of progression after THP (4 to 8 cycles)
- ECOG PS of 0 or 1
- No or asymptomatic BM confirmed by contrast-enhanced MRI at screening

R 1:1

Randomization was stratified by:
- Diagnosis: *de novo* or recurrent
- HR status: positive or negative
- Presence or history of BM: yes or no

1L Maintenance Therapy

TUC 300 mg PO BID + **HP*** Once every 21 days ± ET **(n = 326)**

PBO PO BID + **HP*** Once every 21 days ± ET **(n = 328)**

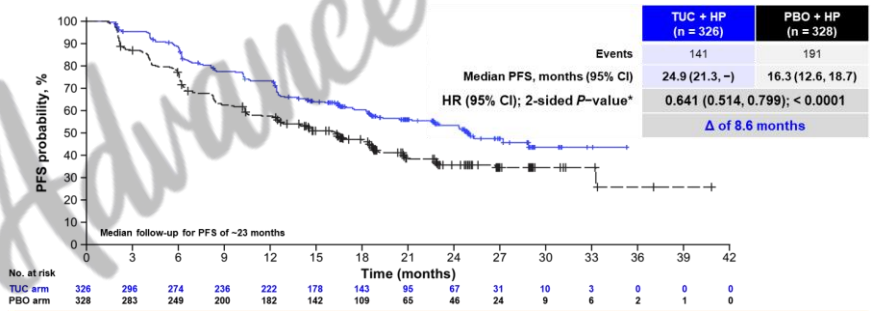
Study treatment continues until unacceptable toxicity, disease progression, consent withdrawal, or study closure. No crossover from PBO to TUC was allowed.

Endpoints

Primary
- Investigator-assessed PFS per RECIST v1.1

Secondary
- OS (key secondary)
- PFS per BICR
- CNS-PFS
- Safety
- HRQoL
- Pharmacokinetics

PFS



	TUC + HP (n = 326)	PBO + HP (n = 328)
Events	141	191
Median PFS, months (95% CI)	24.9 (21.3, –)	16.3 (12.6, 18.7)
HR (95% CI); 2-sided *P*-value*	0.641 (0.514, 0.799); < 0.0001	
	Δ of 8.6 months	

Addition of TUC to 1L maintenance therapy extended median PFS to over 2 years in patients with HER2+ MBC, an **8.6-month** improvement over HP, the standard-of-care.

Baseline characteristics

Characteristics	TUC + HP (n = 326)	PBO + HP (n = 328)
Age, years, median (range)	54.0 (24–82)	54.0 (29–83)
Race, n (%)		
White	147 (45.1)	147 (44.8)
Asian	119 (36.5)	111 (33.8)
Black/African American	10 (3.1)	9 (2.7)
Multiple or other	10 (3.1)	15 (4.6)
Not reportable/unknown	40 (12.3)	46 (14.0)
ECOG PS, n (%)		
0	215 (66.0)	204 (62.2)
1	110 (33.7)	123 (37.5)
HR status, n (%)		
Positive	168 (51.5)	176 (53.7)
Received ET	74 (44.0)	81 (46.0)
Negative	158 (48.5)	152 (46.3)
Presence or history of BM, n (%)	41 (12.6)	40 (12.2)
Visceral disease, n (%)	194 (59.5)	172 (52.4)

Characteristics	TUC + HP (n = 326)	PBO + HP (n = 328)
Disease status, n (%)		
De novo	227 (69.6)	226 (68.9)
Recurrent	99 (30.4)	102 (31.1)
Any prior (neo)adjuvant systemic therapy, n (%)	87 (26.7)	91 (27.7)
Prior trastuzumab*	60 (69.0)	67 (73.6)
Prior pertuzumab*	16 (18.4)	15 (16.5)
Induction HP cycles, median (range)	6 (4–10)	6 (4–11)
Induction T cycles, median (range)	6 (4–9)	6 (3–8)
Best response to induction THP, n (%)		
CR	30 (9.2)	32 (9.8)
PR	204 (62.6)	208 (63.4)
SD	77 (23.6)	75 (22.9)
Non-CR/Non-PD	15 (4.6)	13 (4.0)

Hamilton E, et al. SABCS 2025

Can we optimize the Cleopatra strategy?

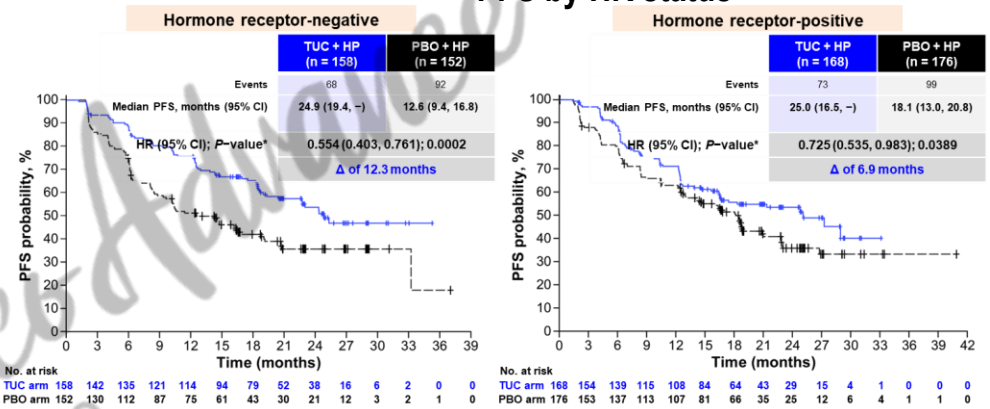
HER2CLIMB-05 Trial

PFS in prespecified subgroups

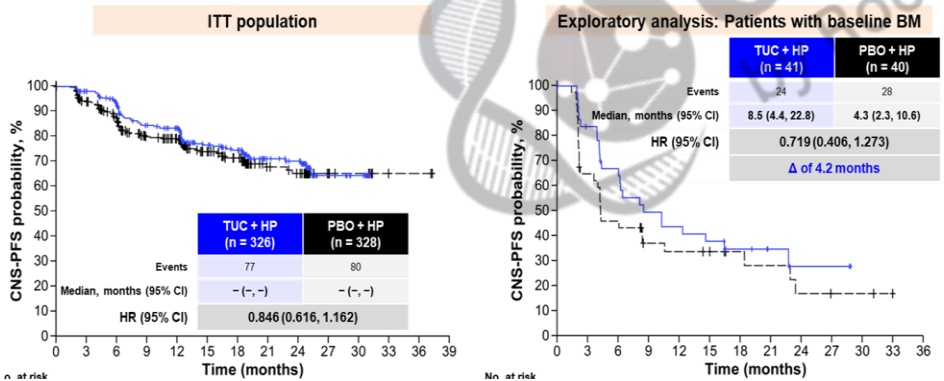
Patient Groups		TUC + HP Events/No.	PBO + HP Events/No.	TUC + HP vs PBO + HP HR (95% CI)
	ITT analysis	141/326	191/328	0.641 (0.514, 0.799)
Diagnosis	De novo	93/227	129/226	0.621 (0.475, 0.813)
	Recurrent	48/99	62/102	0.671 (0.457, 0.986)
Hormone receptor status	Negative	68/158	92/152	0.554 (0.403, 0.761)
	Positive	73/168	99/176	0.725 (0.535, 0.983)
Brain metastases at baseline	Yes	26/41	34/40	0.640 (0.373, 1.097)
	No	115/285	157/288	0.640 (0.503, 0.816)
Prior anti-HER2 therapy	Yes	27/62	45/69	0.569 (0.347, 0.934)
	No	114/264	146/259	0.666 (0.519, 0.854)
Best response to induction THP	CR or PR	101/234	135/240	0.695 (0.535, 0.902)
	SD or Non-CR/Non-PD	40/92	56/88	0.594 (0.377, 0.938)
Disease type	Visceral	96/194	107/172	0.642 (0.484, 0.852)
	Nonvisceral	45/132	84/156	0.561 (0.387, 0.813)
ECOG PS	0	89/215	114/204	0.637 (0.480, 0.846)
	1	52/110	76/123	0.591 (0.408, 0.857)
Region	North America	14/41	23/48	0.808 (0.392, 1.667)
	Europe	52/116	66/114	0.769 (0.529, 1.117)
	Asia−Pacific	47/121	70/113	0.469 (0.320, 0.688)
	Rest of World	28/48	32/53	0.710 (0.408, 1.233)
Age, years	< 65	124/274	161/272	0.655 (0.517, 0.831)
	≥ 65	17/52	30/56	0.447 (0.226, 0.883)
Race	White	68/147	81/147	0.829 (0.596, 1.153)
	Asian	48/119	70/111	0.481 (0.329, 0.702)
	Other	25/60	40/70	0.576 (0.339, 0.978)

Favors TUC + HP ← 0.1 1.0 10.0 → Favors PBO + HP

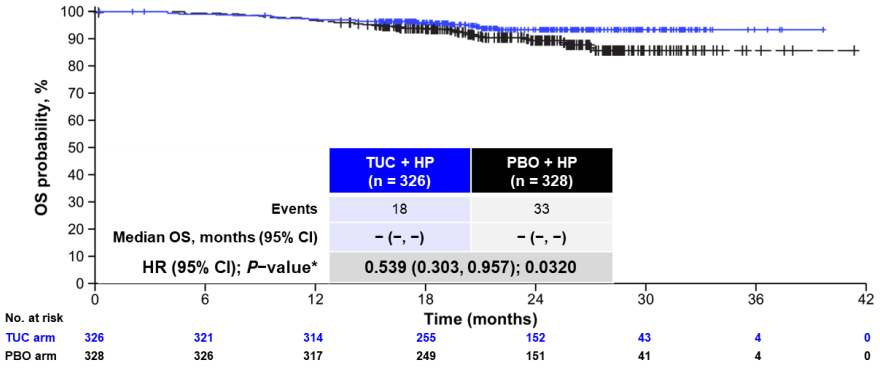
PFS by HR status



CNS-PFS

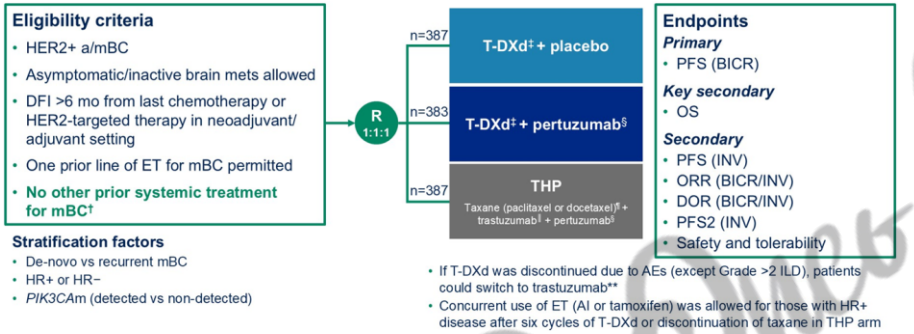


OS



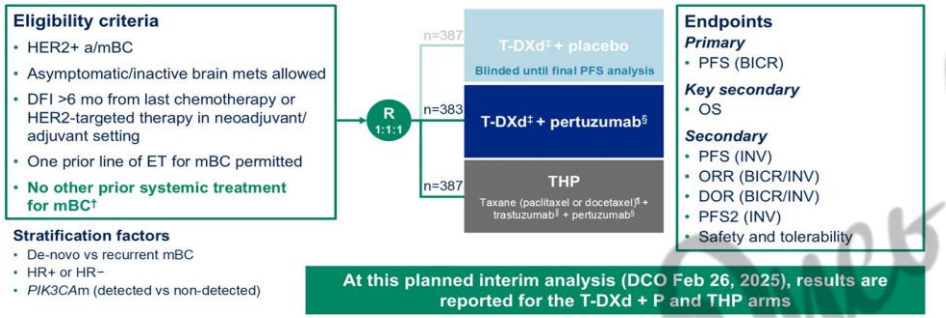
Hamilton E, et al. SABCS 2025

Trastuzumab Deruxtecan in “first-line” Destiny-Breast 09 study



Tolaney S,. et al. ASCO 2025

Trastuzumab Deruxtecan in “first-line” Destiny-Breast 09 study



Tolaney S,. et al. ASCO 2025

Trastuzumab Deruxtecan in “first-line” Destiny-Breast 09 study

Eligibility criteria
- HER2+ a/mBC
- Asymptomatic/inactive brain mets allowed
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant/ adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic treatment for mBC†**

Stratification factors
- De-novo vs recurrent mBC
- HR+ or HR−
- *PIK3CA*m (detected vs non-detected)

R 1:1:1

- n=387: T-DXd‡ + placebo — Blinded until final PFS analysis
- n=383: T-DXd‡ + pertuzumab§
- n=387: THP — Taxane (paclitaxel or docetaxel)§ + trastuzumab§ + pertuzumab§

Endpoints

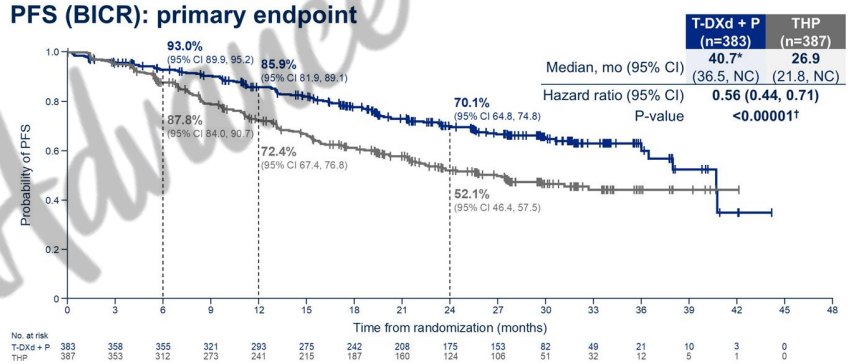
Primary
- PFS (BICR)

Key secondary
- OS

Secondary
- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerability

At this planned interim analysis (DCO Feb 26, 2025), results are reported for the T-DXd + P and THP arms

PFS



Tolaney S,. et al. ASCO 2025

Trastuzumab Deruxtecan in “first-line” Destiny-Breast 09 study

Clinical Trial Design (DB03)

Eligibility criteria
- HER2+ a/mBC
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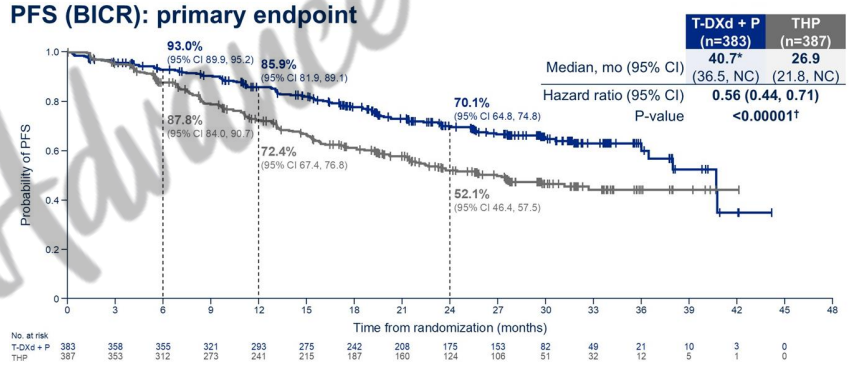
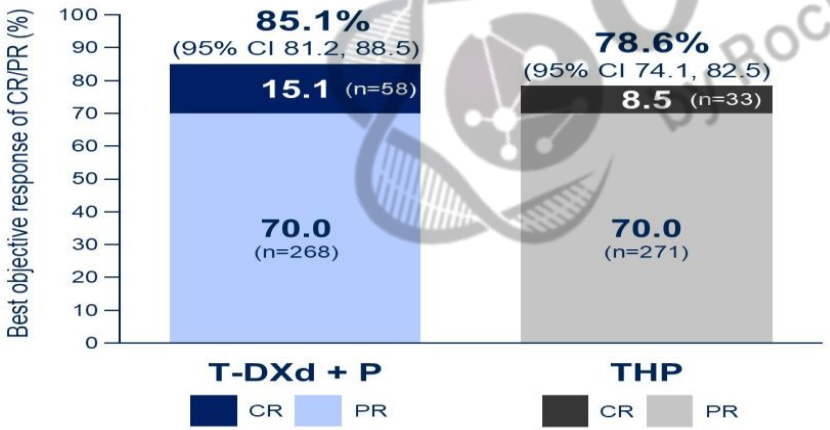
PFS



ORR



Tolaney S,. et al. ASCO 2025

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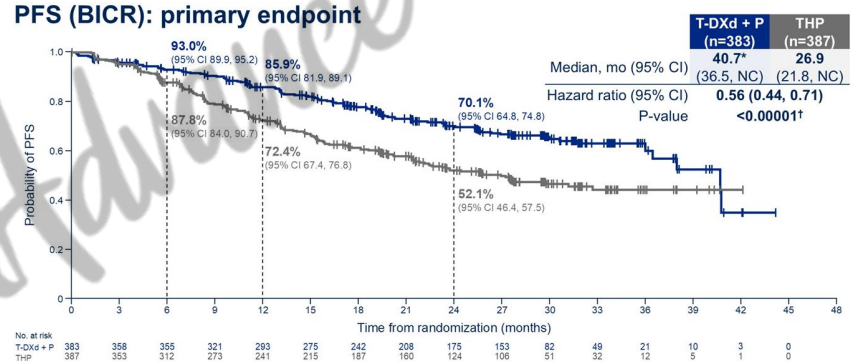
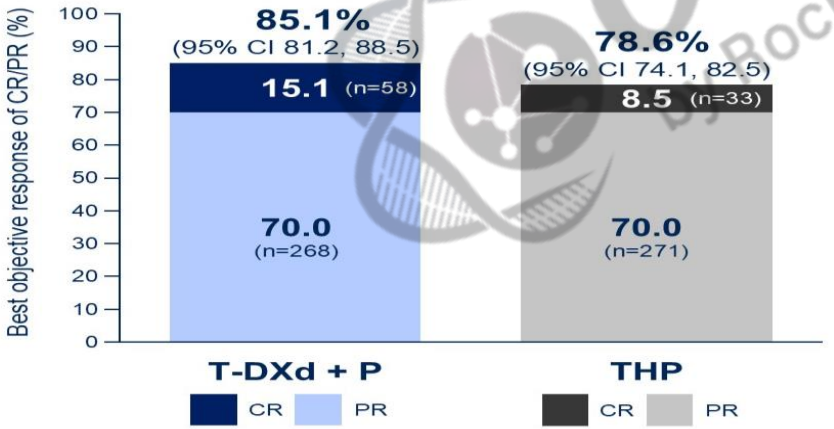
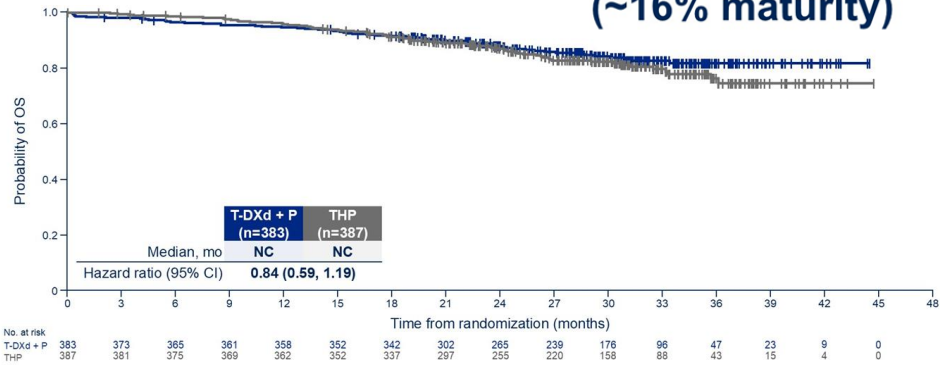
PFS



ORR



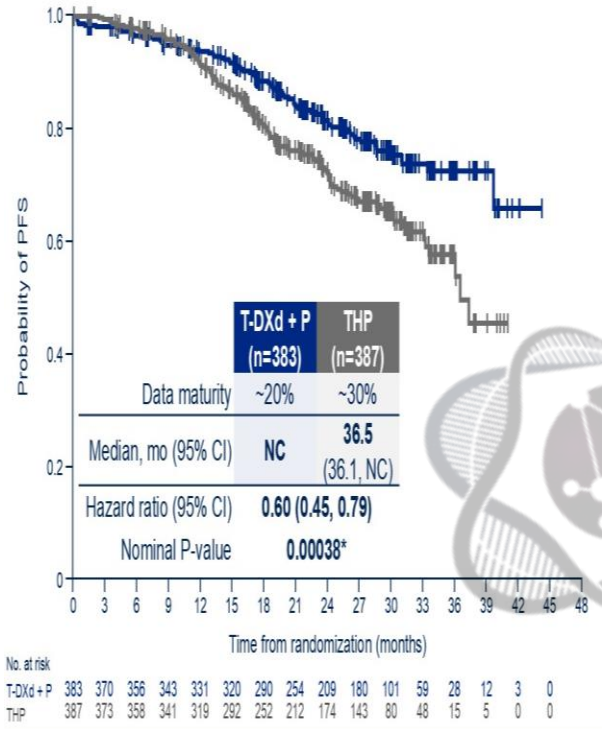
OS (~16% maturity)



Tolaney S,. et al. ASCO 2025

Trastuzumab Deruxtecan in “first-line” Destiny-Breast 09 study

PFS-2



	T-DXd + P (n=383)	THP (n=387)
Data maturity	~20%	~30%
Median, mo (95% CI)	NC	**36.5** (36.1, NC)
Hazard ratio (95% CI)	**0.60 (0.45, 0.79)**	
Nominal P-value	**0.00038***	

	T-DXd + P (n=383)	THP (n=387)
Received post-discontinuation therapy in second line, n (%)†	124 (32.4)	181 (46.8)
Targeted therapy, n (%)†	111 (29.0)	166 (42.9)
T-DXd	6 (1.6)	39 (10.1)
T-DM1	7 (1.8)	47 (12.1)
Trastuzumab-containing regimen‡	78 (20.4)	51 (13.2)
Pertuzumab-containing regimen‡	53 (13.8)	34 (8.8)
Chemotherapy, n (%)†	68 (17.8)	57 (14.7)
Docetaxel	24 (6.3)	8 (2.1)
Paclitaxel	18 (4.7)	4 (1.0)
Capecitabine	24 (6.3)	35 (9.0)
Endocrine therapy, n (%)†	19 (5.0)	13 (3.4)

AESI

Adjudicated drug-related ILD/pneumonitis*

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd + P (n=381)	17 (4.5)	27 (7.1)	0	0	2 (0.5)	46 (12.1)
THP (n=382)	2 (0.5)	2 (0.5)	0	0	0	4 (1.0)

Left ventricular dysfunction†

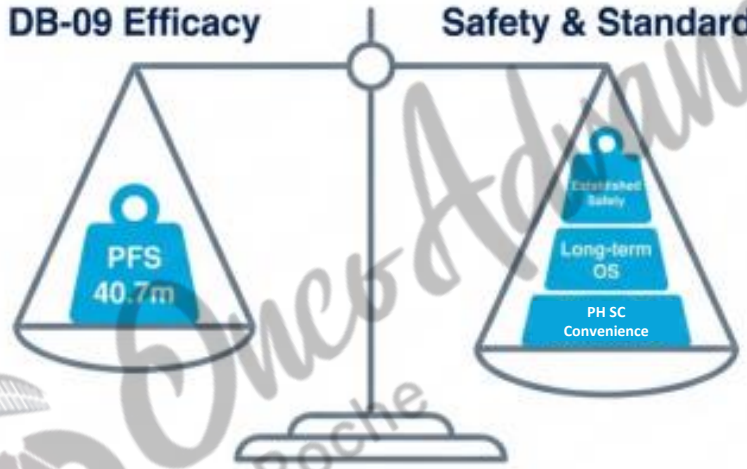
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd + P (n=381)	4 (1.0)	30 (7.9)	7 (1.8)	1 (0.3)	0	42 (11.0)
THP (n=382)	1 (0.3)	19 (5.0)	7 (1.8)	0	0	27 (7.1)

Tolaney S,. et al. ASCO 2025

The Safety Trade Off: Why Guideline Prioritize The Taxane Backbone

T-DXd + Pertuzumab[1]

- ILD/ Pneumonitis: 12.1% (including 2 grade 5 death)
- High hematologic toxicity (neutropenia, Anemia)



THP[2]

- ILD/ Pneumonitis: 1% (all grade 1-2)
- Manageable, reversible toxicity profie

The Risk of ILD (12.1%) with T-DXd + P presents a significant monitoring burden.
THP offers an optimal balance of OS benefit & safety

1.Tolaney SM et al. Trastuzumab Deruxtecan plus Pertuzumab for HER2-Positive Metastatic Breast Cancer . NEJM; Published online 29 October 2025. DOI: 10.1056/NEJMoa2508668. 2 Baselga J, *et al. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. N Engl J Med* 2012; **366:**109–119; 3. Swain SM, *et al. N Engl J Med* 2015; **372:**724–734; 3. Swain SM, *et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study Lancet Oncol* 2020; **21:**519–530.

If T-DXd is prescribed in 1L, what is the optimal duration of T-DXd + P therapy and can an induction–maintenance strategy be considered?

Median time to response with 3L+ T-DXd in DESTINY-Breast01[1]

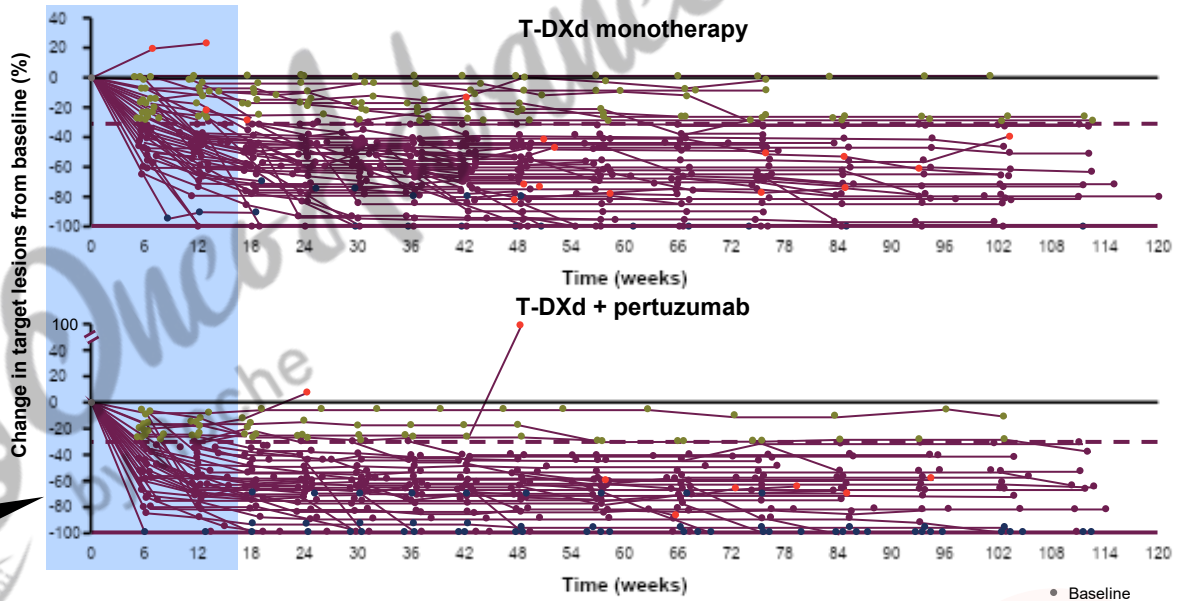
1.6 months
(95% CI = 1.4, 2.6)

Median time to response (first CR/PR) with 2L+ T-DXd* in DESTINY-Breast03[2]

1.6 months
(95% CI = 1.1, 17.1)

Majority of responses were seen by Week 12 and were durable

Percentage change in target lesions from baseline in DESTINY-Breast07[3]

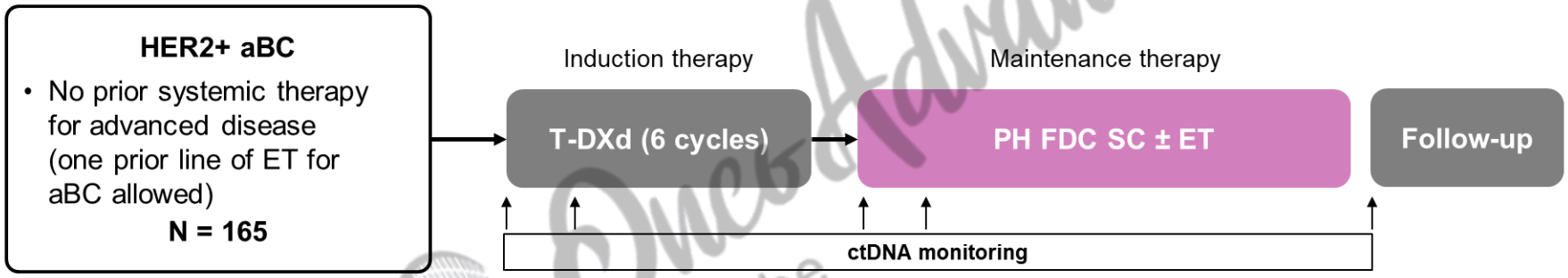


- Most of the objective responses occurred in early cycles;[1–3] patients who do not respond early tend not to respond with longer treatment
- Median duration of T-DXd treatment was substantially shorter than median PFS[1,2]
- Optimal treatment duration is an important consideration to maximise tolerability whilst maintaining efficacy

. Modi S, *et al*. *N Engl J Med* 2020; 2. Cortés J, *et al*. *N Engl J Med* 2022; 3. André F, *et al*. ASCO 2024

DEMETHER will inform the feasibility of a T-DXd induction–PH FDC SC maintenance approach in patients with HER2+ aBC

DEMETHER: Phase II study of 1L T-DXd induction followed by maintenance PH FDC SC[1,2]



Primary endpoints
- 1-year PFS, 3-year OS

DEMETHER results will complement DESTINY-Breast09, aiming to build on CLEOPATRA in terms of cytotoxic induction therapy duration while taking into consideration the time to best response with T-DXd, to help optimise efficacy, tolerability and QoL for patients treated in the 1L setting

PI, J Cortes

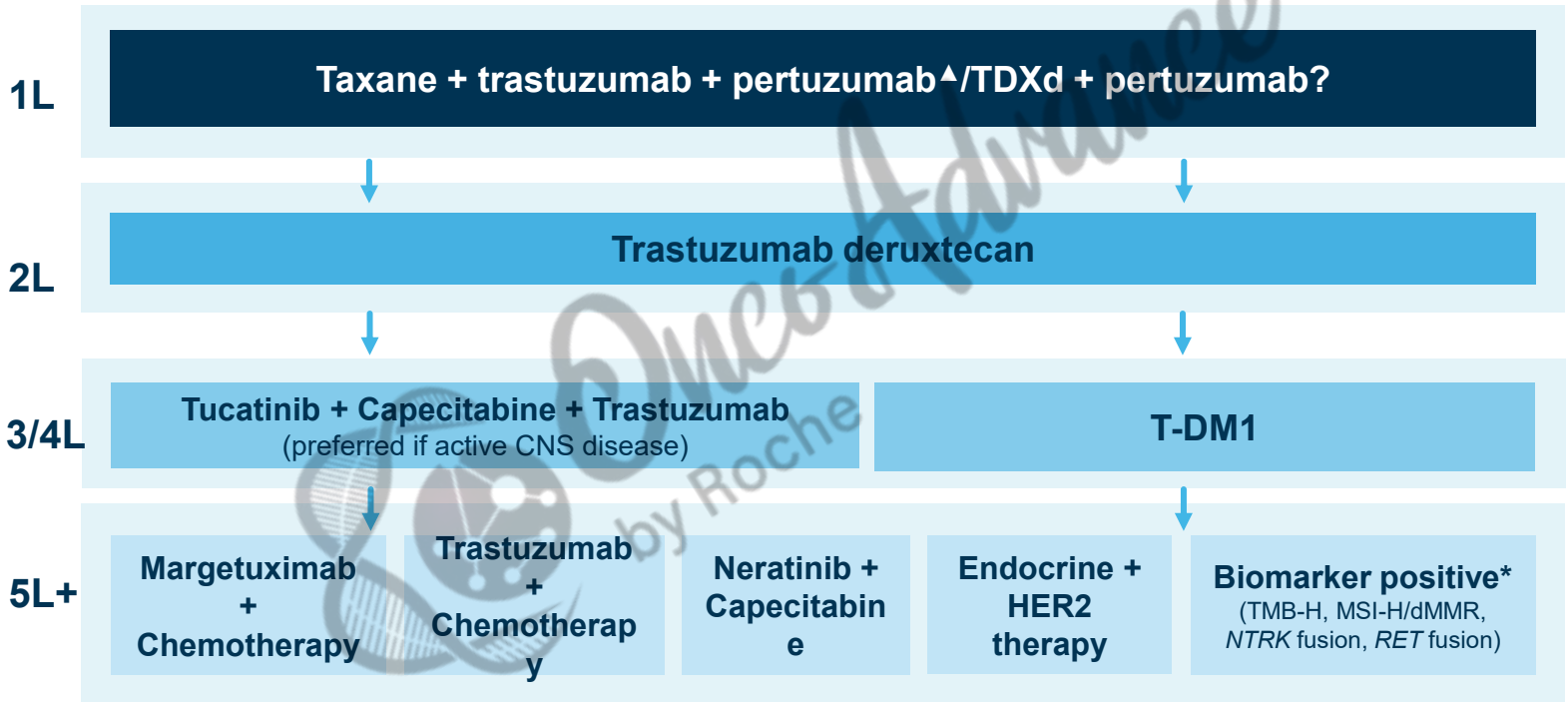
Third-generation ADCs in pretreated HER2+ MBC: Phase 3 studies

	Trastuzmb botidotin	Destiny-Breast 03[2]	Destiny-Breast 02[3]	ACE-Breast-02[4]	TULIP[5]
ADC Payload (MoA)	Trastuzumab botidotin Tubulin Inhibitor	Trastuzumab Deruxtecan Topo I Inhibitor	Trastuzumab Deruxtecan Topo I Inhibitor	ARX-788 Tubulin Inhibitor	Trastuzmb Duocarmazine DNA-alkylating
Control Arm	T-DM1	T-DM1	Lapatinib (o trastuzumab) + capecitabine	Lapatinib + capecitabine	TPC
N (Experimental arm)	182	261	406	221	230
Prior anti-HER2 lines in MBC (1 vs >1) (%)	46 vs 54	~50* vs 50	~0 vs ~100	67 vs 33	Majority (>1)
Prior Pertuzumab	46%	62%	78%	34%	61%
Prior T-DM1	0%	0%	100%	0%	>85%
Primary Objective	PFS by BICR*	PFS by BICR	PFS by BICR & OS	PFS by BICR	PFS by BICR
ORR	76.9%	79.7%	69.7%	63.8%	28
PFS (HR & 95% CI) Median PFS (mo)	0.39 (0.30-0.51) 11.1 mo	0.33 (0.26-0.43) 28.8 mo	0.36 (0.28-0.45) 17.8 mo	0.64 (0.49-0.82) 11.3 mo	0.64 (0.49-0.84) 7.0 mo
OS (HR & 95% CI) Median OS (mo)	0.62 (0.38-1.03) NR	0.73 (0.56-0.94) 52.6 mo	0.66 (0.50-0.86) 39.2 mo	0.71 (0.46-1.10) NR	0.87 (0.68-1.12) 21 mo

- 2 patients were treated in 1st Line
- Abbr: BICR, Blinded Independent Central Review; NR, not reached; OS, overall survival; ORR, overall response rate; PFS, progression-free surviva; TPC: Treatment of Physician's Choice

1. Hu X, et al. ESMO 2025; 2. Cortes J, et al Nat Med 2024; 3. Andre F, et al. Lancet 2023; 4. Hu X, et al. Signal Transduct Target Ther 2025; 5. Turner N, et al. JCO 2025

Treatment algorithm in HER2+ MBC (with no CNS involvement)



▲Maintenance HER2-targeted therapy (+ endocrine therapy if HR+) after response.
*TMB-H: Pembrolizumab; MSI-H: Pembrolizumab, Dostarlimab; NTRK fusion: Larotrectinib, Entrectinib; RET fusion: Selpercatinib

Courtesy Garrido-Castro A (modified)

How to start? Which is the optimal first-line strategy?

1L | **Taxane + trastuzumab + pertuzumab▲/TDXd + pertuzumab?**

▲Maintenance HER2-targeted therapy (palbociclib/tucatinib) (+ endocrine therapy if HR+) after response.

Clinical Trial Design (DB09)

Eligibility criteria
- HER2+ a/mBC
- Asymptomatic/inactive brain mets allowed
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant/adjuvant setting
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- PFS2 (INV)
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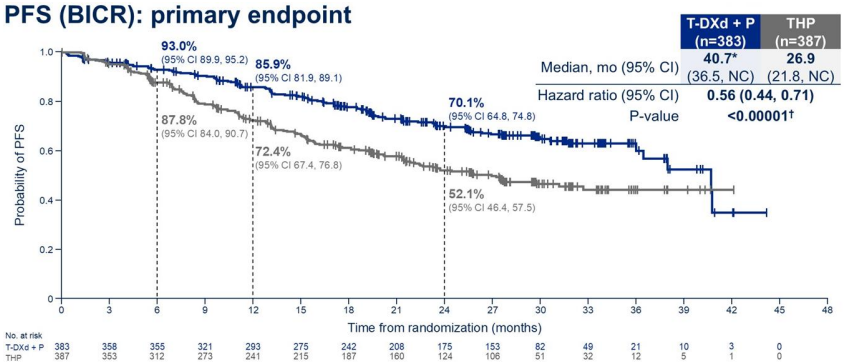
PFS



Javier Cortés, MD, PhD

Tolaney S, et al. ESMO 2025

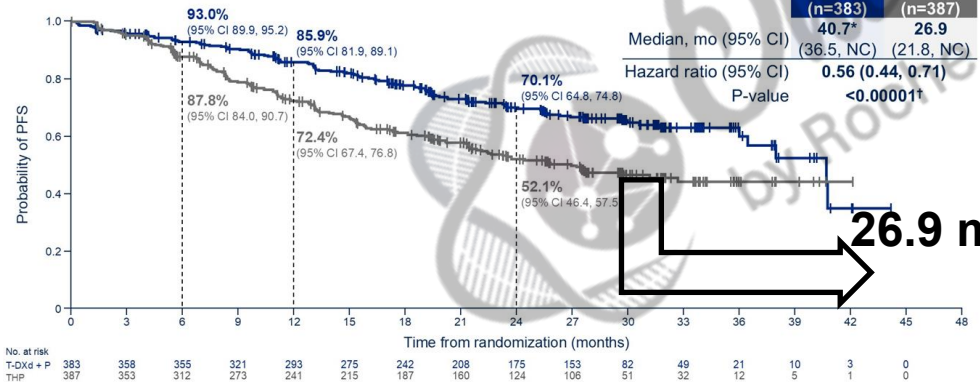
How to start? Which is the optimal first-line strategy?

1L | **Expected mPFS2?**

▲ **Without** Maintenance HER2-targeted therapy (palbociclib/tucatinib) (+ endocrine therapy if HR+) after response.

PFS (DB09) **40.7 m**

PFS (BICR): primary endpoint



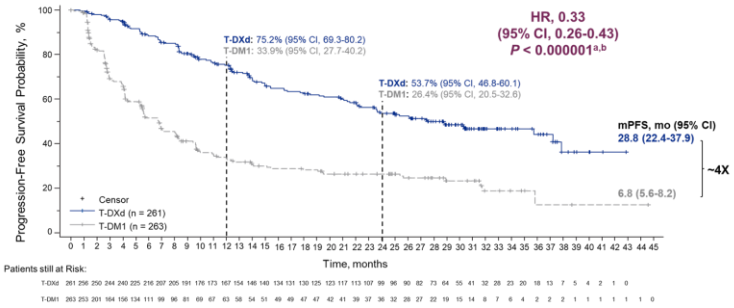
	T-DXd + P (n=383)	THP (n=387)
Median, mo (95% CI)	40.7* (36.5, NC)	26.9 (21.8, NC)
Hazard ratio (95% CI)	0.56 (0.44, 0.71)	
P-value	<0.00001†	

26.9 m

<7 m ?

26.0 m

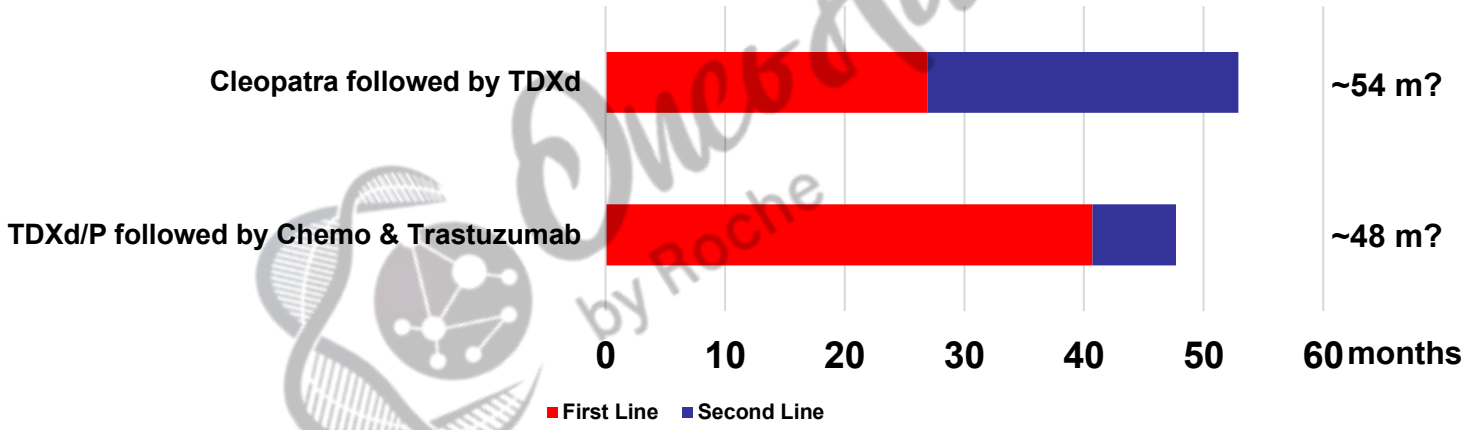
PFS (DB03)
PFS **28.8 m**



How to start? Which is the optimal first-line strategy?

1L Taxane + trastuzumab + pertuzumab▲/TDXd + pertuzumab?

Starting with Cleopatra vs TDXd+ Pertuzumab



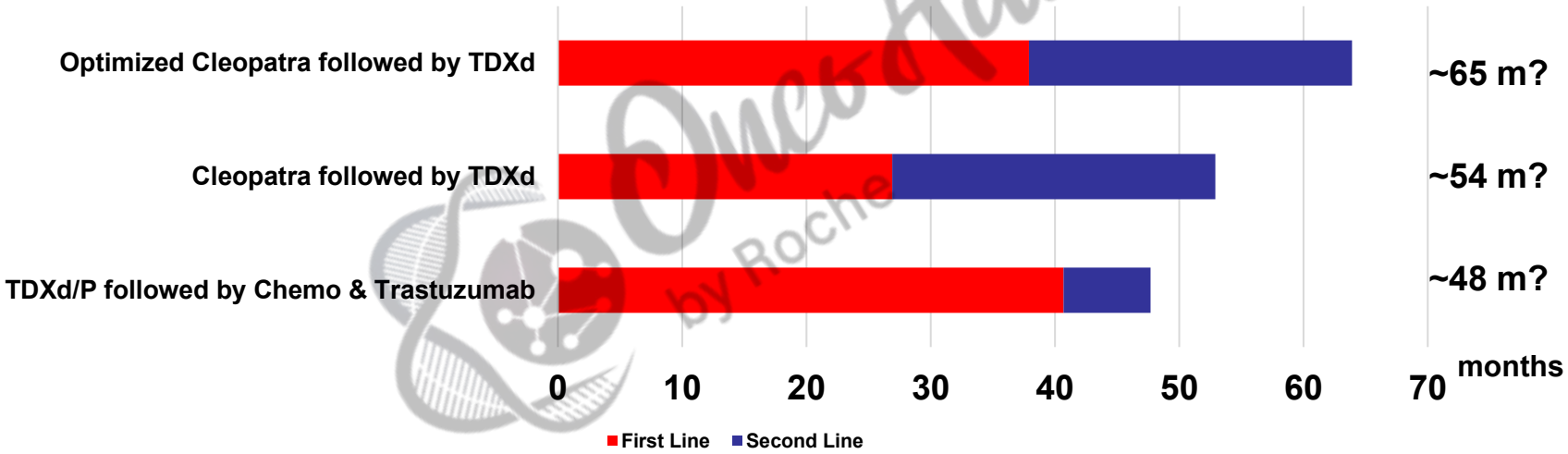
Javier Cortés, MD, PhD

Tolaney S, et al. ESMO 2025

How to start? Which is the optimal first-line strategy?

1L Taxane + trastuzumab + pertuzumab▲/TDXd + pertuzumab?

Starting with Cleopatra vs TDXd+ Pertuzumab (optimized)

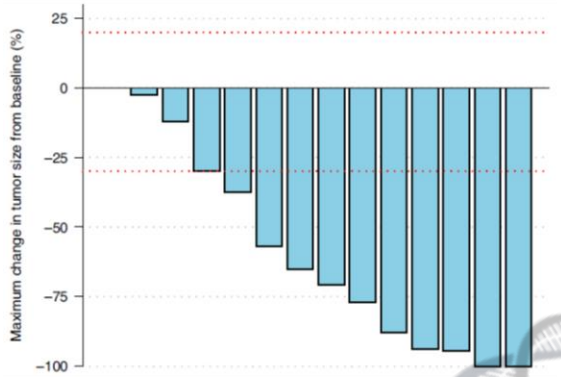


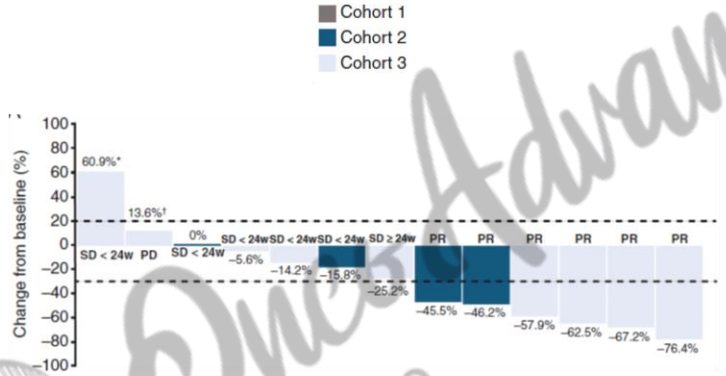
Javier Cortés, MD, PhD

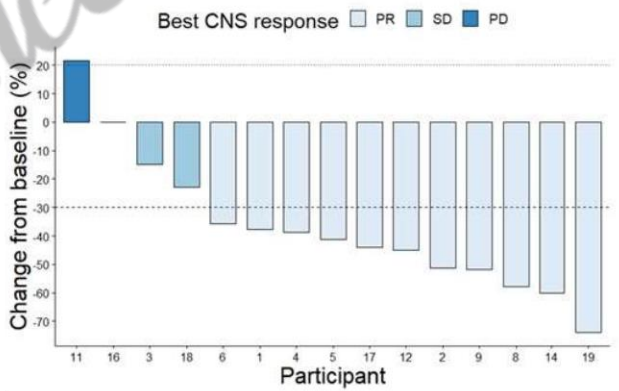
Tolaney S, et al. ESMO 2025

HER2+ BC & unstable Brain Metastases

Trastuzumab Deruxtecan & Active Brain Mets (HER2+)







TUXEDO-1[1]
Active BM; newly diagnosed and progressive
RR 73.3%

DEBBRAH[2]
Cohort 2 *de novo* BM; cohort 3 progressive BM
RR 46.2%

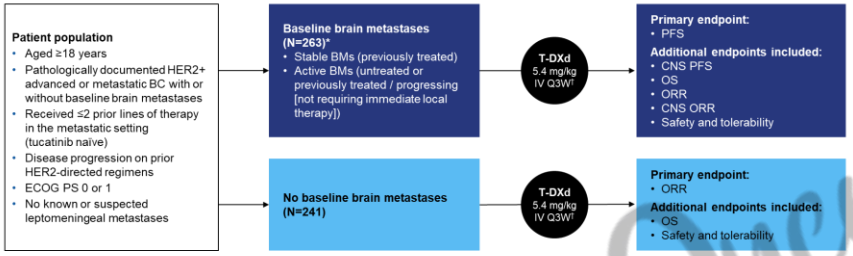
DFCI/Duke/MDACCC series[3]
70% active BM
RR 73%

Bartsch R, et al. Nat Med; Perez-Garcia J, et al. Neuro Oncol 2023; Kabraji S, et al. Clin Cancer Res 2023

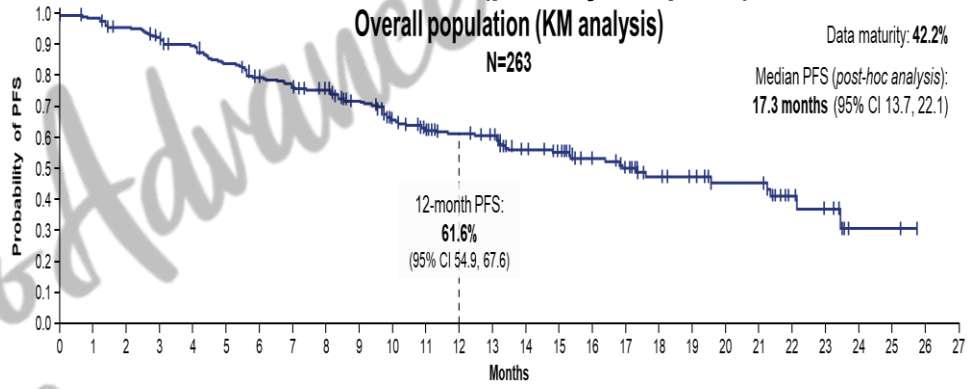
Trastuzumab Deruxtecan & Brain Mets (HER2+)
Destiny-Breast 12

DB12- Study Design

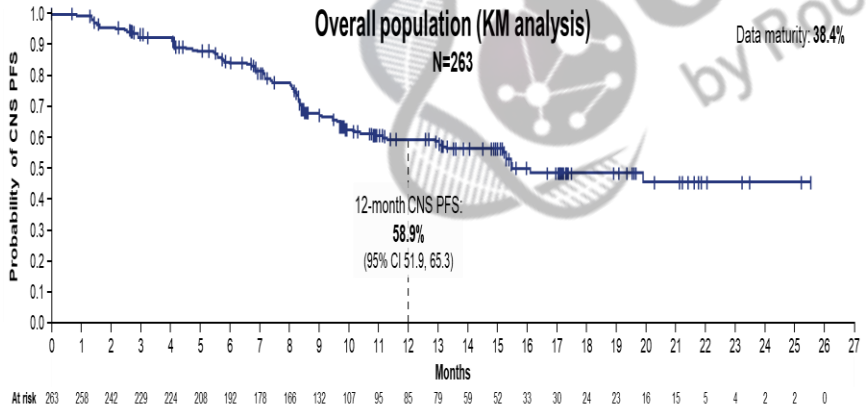
Phase 3b/4, multicenter, single-arm, two-cohort, open-label study of T-DXd in previously treated HER2+ mBC with and without brain metastases (BMs); the largest prospective study of T-DXd in patients with stable or active BMs



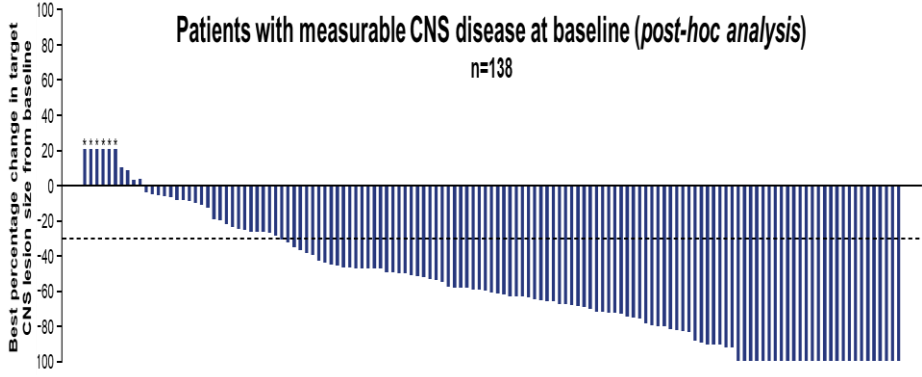
Baseline BMs: PFS (primary endpoint)



Baseline BMs: CNS PFS



Baseline BMs: CNS ORR

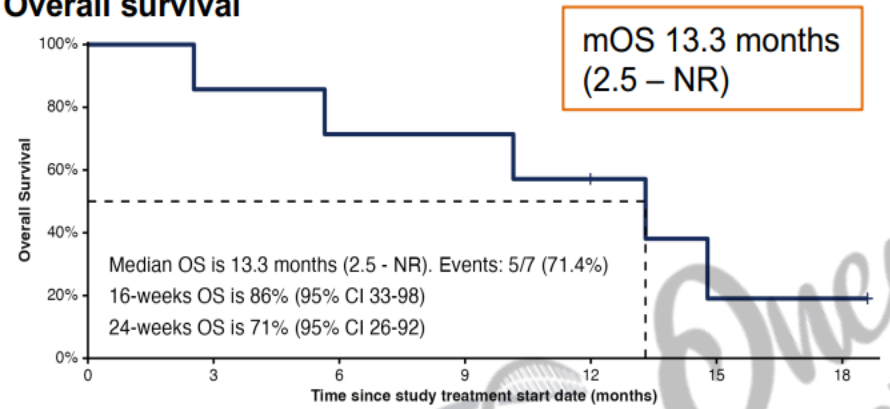


Lin N, et al. ESMO 2024; Karbeck N, et al. Nat Med 2024

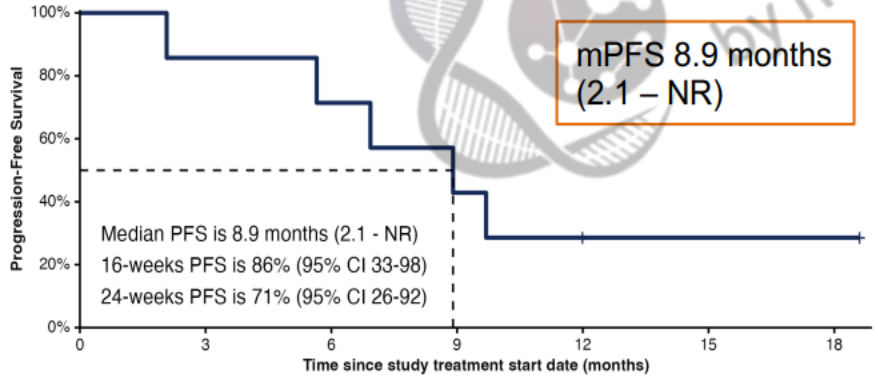
TDXd in pathological confirmed LMC: DEBBRAH study

HER2 status: Positive 3 (42.9%) Low 4 (57.1%)

Overall survival



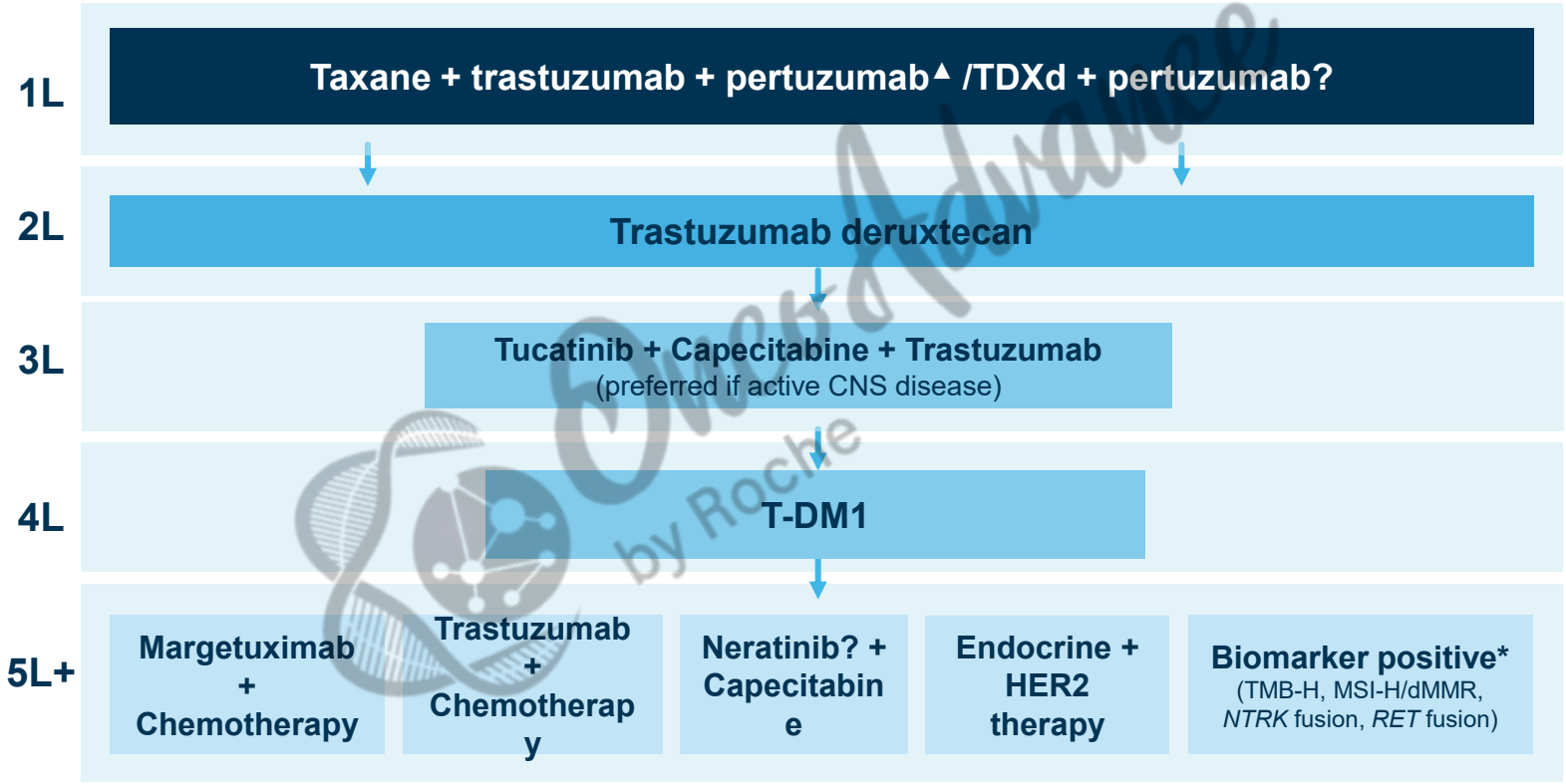
PFS according to RANO-BM and RECIST v1.1



	Intracranial	Extracranial	All lesions
Best Overall Response	n = 7	n = 7	n = 7
CR	1 (14.3%)	0 (0%)	0 (0%)
SD ≥ 24w	1 (14.3%)	2 (28.6%)	2 (28.6%)
SD < 24w	0 (0%)	0 (0%)	0 (0%)
Non-CR/Non-PD ≥ 24w	2 (28.6%)	3 (42.9%)	3 (42.9%)
Non-CR/Non-PD < 24w	1 (14.3%)	0 (0%)	1 (14.3%)
PD	0 (0%)	1 (14.3%)	1 (14.3%)
NE	2 (28.6%)	1 (14.3%)	0 (0%)
Objective Response Rate (ORR)	n = 5	n = 6	n = 7
Yes	1 (20%)	0 (0%)	0 (0%)
No	4 (80%)	6 (100%)	7 (100%)
Clinical Benefit Rate (CBR)	n = 5	n = 6	n = 7
Yes	4 (80%)	5 (83.3%)	5 (71.4%)
No	1 (20%)	1 (16.7%)	2 (28.6%)

Vaz M, et al. SABCS 2023; Vaz M, et al. Med 2025

Treatment algorithm in HER2+ MBC (if CNS involvement-My opinion)



▲Maintenance HER2-targeted therapy (+ endocrine therapy if HR+) after response.
*TMB-H: Pembrolizumab; MSI-H: Pembrolizumab, Dostarlimab; NTRK fusion: Larotrectinib, Entrectinib; RET fusion: Selpercatinib

Courtesy Garrido-Castro A (modified)