



**2024 Breast Cancer Congress**

with Updates from the 2023 SABCS

**Friday, February 2, 2024**

4:00 PM – 4:25 PM CST

# Advances in the Management of HER2-Positive Metastatic Breast Cancer with SABCS Updates

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# Outline

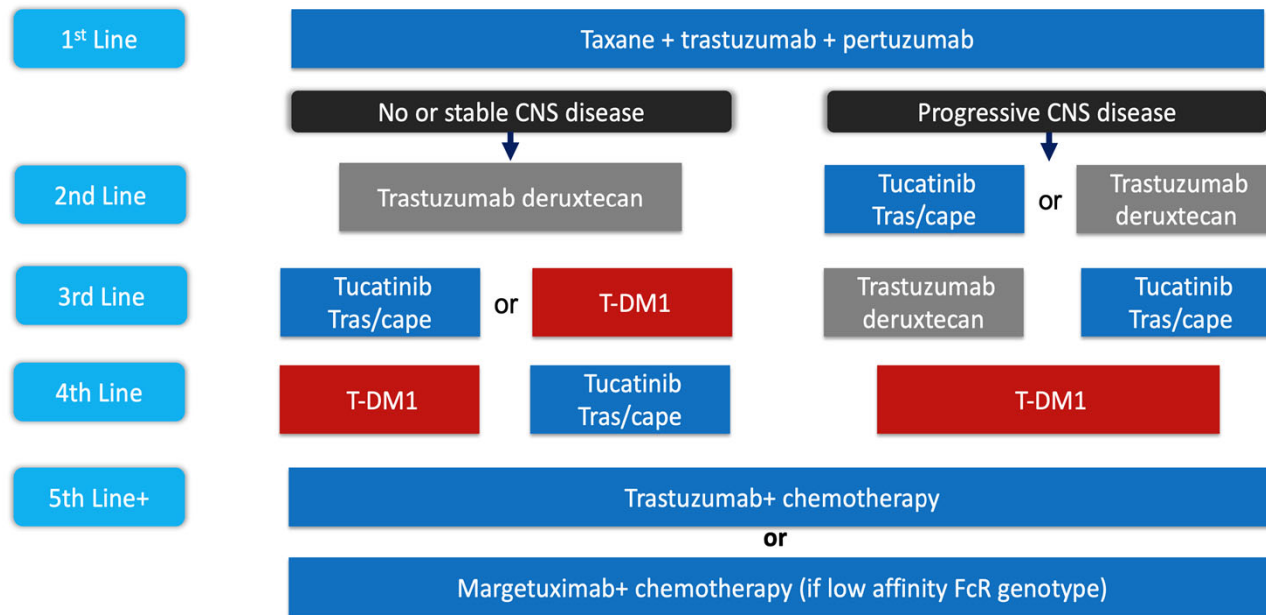
- Current standards for HER2+ MBC
- Will TXD-d move up to 1<sup>st</sup> line?
- Can the efficacy of tucatinib be enhanced with a ADC?
- Potpourri of HER2 CNS issues



**SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE<sup>k</sup>**

HR-Positive or -Negative and HER2-Positive <sup>l,k</sup>	
Setting	Regimen
First Line <sup>l</sup>	Pertuzumab + trastuzumab + docetaxel (Category 1, preferred)
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second Line <sup>n</sup>	Fam-trastuzumab deruxtecan-nxki <sup>m</sup> (Category 1, preferred)
Third Line	Tucatinib + trastuzumab + capecitabine <sup>n</sup> (Category 1, preferred)
	Ado-trastuzumab emtansine (T-DM1) <sup>o</sup>
Fourth Line and Beyond (optimal sequence is not known) <sup>p</sup>	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents <sup>q,r</sup>
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
	Targeted Therapy Options <a href="#">BINV-Q (6)</a>

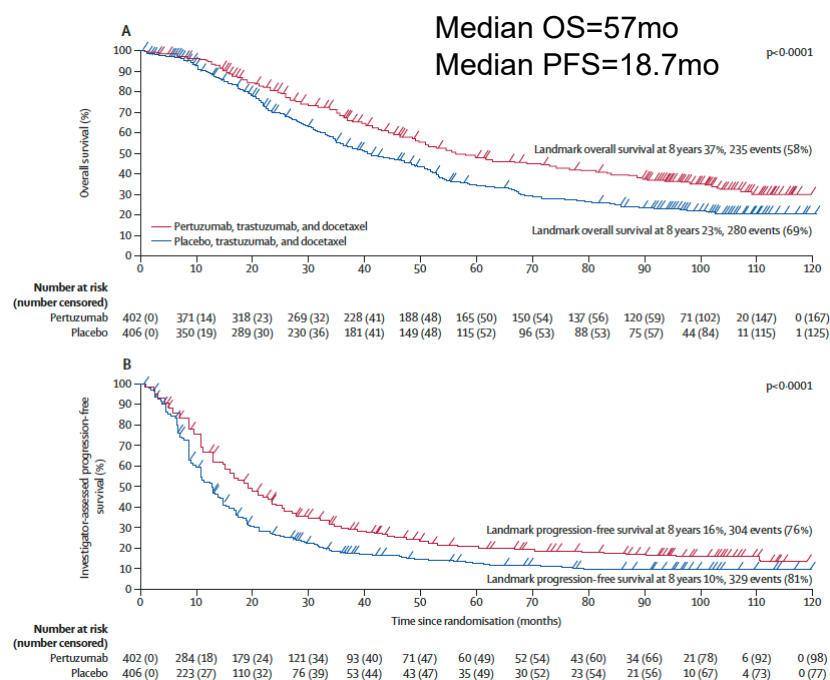
# Approach to Therapy for Metastatic HER2+ disease 2024



Multiple lines of concurrent CT with HER2-directed therapy offers clinical benefit for patients with recurrent HER2+ MBC, but optimal sequencing is not known

Adapted from Modi et al, ESMO 2021

## Long term responders from Cleopatra study



Long term responders: 37% alive and 16% progression free at 8yrs

More likely to be

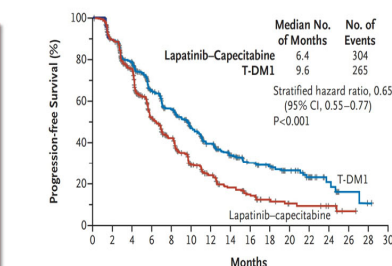
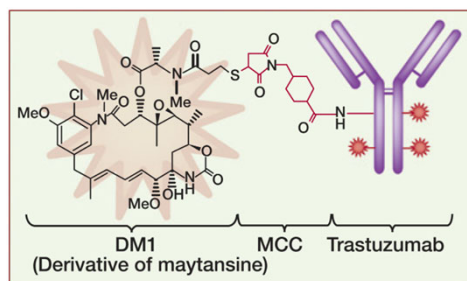
- PR+
- HER2 +3 IHC
- De novo presentation
- have non measurable, non-visceral disease (oligometastatic)
- Tumor *PIK3CA* WT
- Higher HER2 mRNA
- Higher TIL

Swain et al, Lancet Oncology 2020 Median FU 99mo

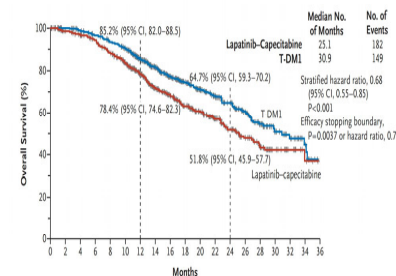
# Phase 3 EMILIA: T-DM1 in HER2+ MBC

In EMILIA, T-DM1 was superior to lapatinib + capecitabine in HER2+ MBC

- In 991 randomized patients, median PFS was 9.6 months with T-DM1 vs 6.4 months with lapatinib + capecitabine (HR 0.65; 95% CI, 0.55-0.77;  $P < .001$ ), and median OS was 30.9 months vs 25.1 months (HR, 0.68; 95% CI, 0.55-0.85;  $P < .001$ )



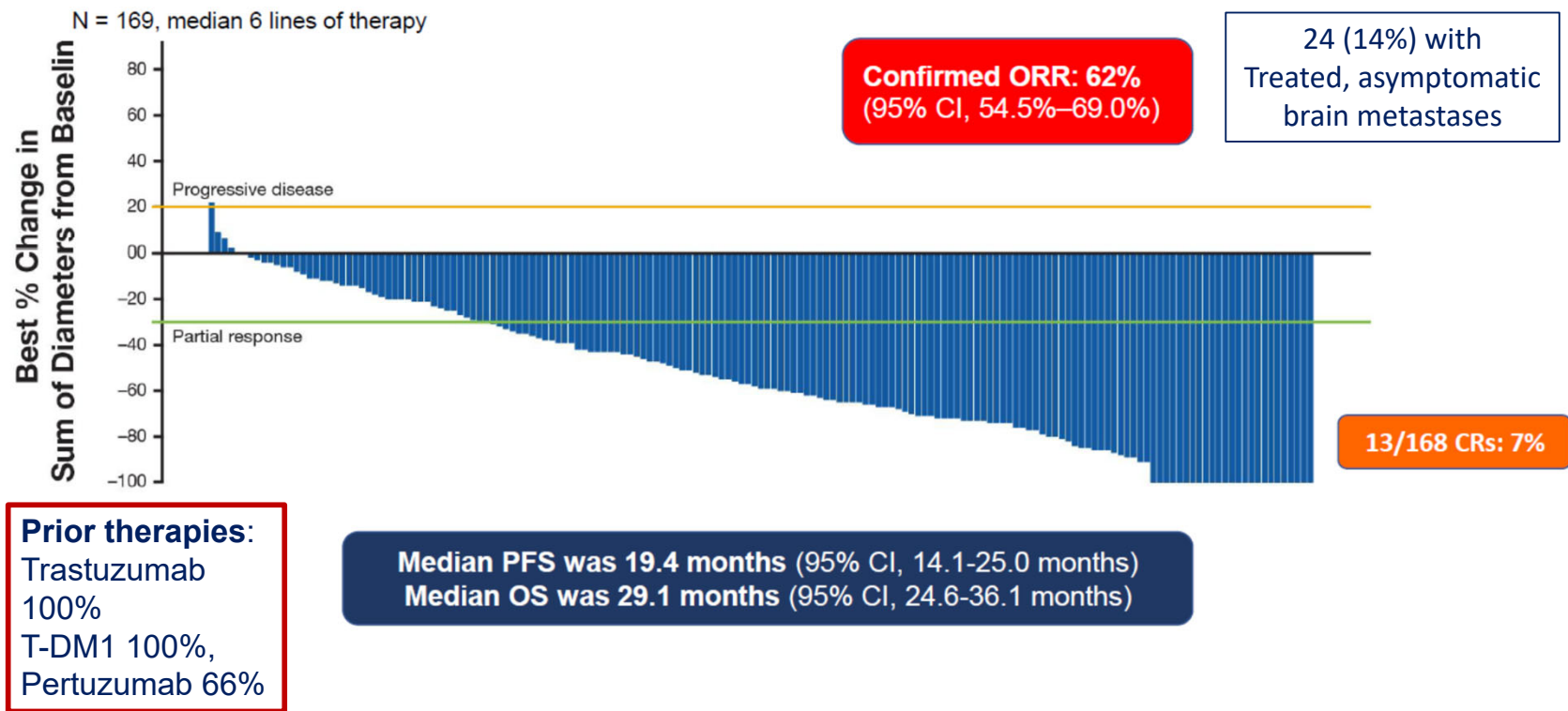
No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Lapatinib-capecitabine	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0



No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Lapatinib-capecitabine	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

Verma S et al. *N Engl J Med*. 2012;367:1783.

## DESTINY-Breast01: Phase 2 Study of T-DXd in HER2+ MBC (Updated Results With 26.5 mo Follow-Up)



NEJM 2020;382:610-21

## Destiny Breast-03: mHER2+ TDXd vs TDM-1 Updated Analysis

### Demographics

- 50% HR+
- 15% baseline brain mets
- 70% visceral disease
- 61% prior pertuzumab
- Median 2 lines of prior therapy

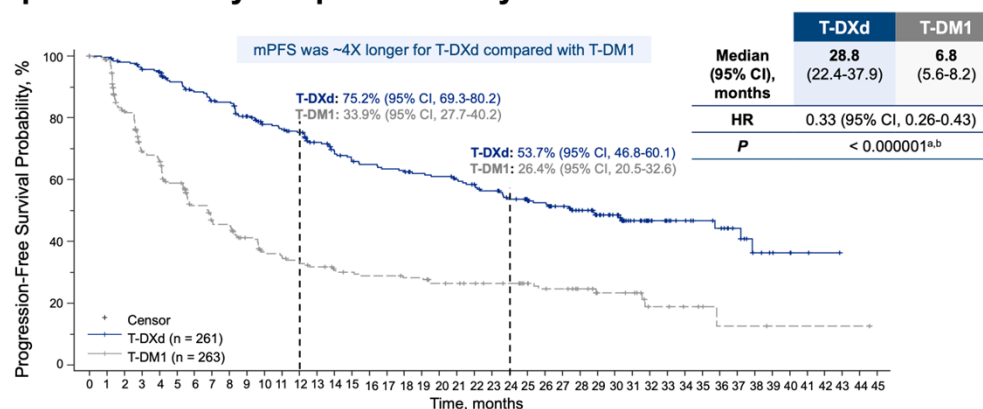
### Anti-cancer therapies in post-trial setting:

- **T-DXd arm:** 64/182 (35.2%) received T-DM1
- **T-DM1 arm:** 42/243 (17.3%) received T-DXd

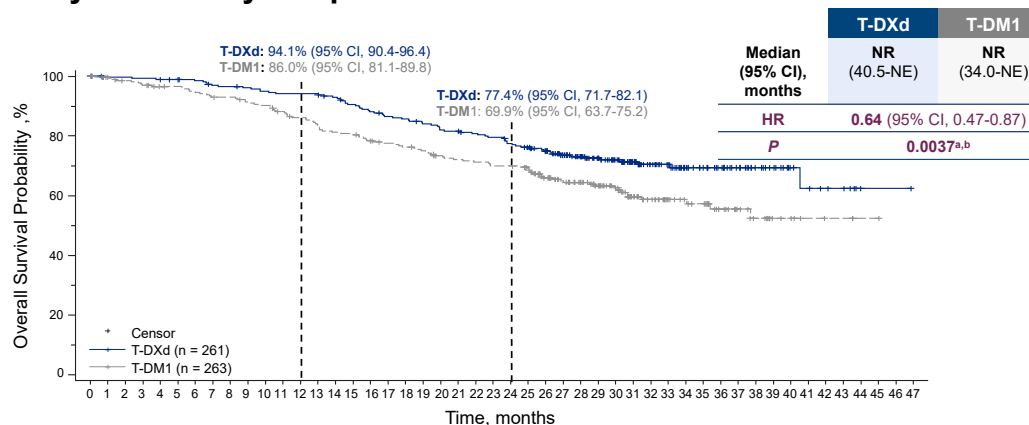
### Updated AEs

- ILD: 15.2%, no grade 4 or 5
- All grade AE
- Nausea: 77%
- Vomiting: 52%
- Alopecia 40%
- Neutropenia  $\geq$  grade 3: 16%

### Updated Primary Endpoint: PFS by BICR



### Key Secondary Endpoint: Overall Survival



Hurvitz S et al. SABCS 2022; Lancet Oncology 2023



# ADCs in sequence?.....benefit?

# DESTINY-Breast02:mHER2+ later line T-DXd vs T-DM1

Randomized phase 3, open-label, multicenter study (NCT03523585)

## Key eligibility criteria<sup>a</sup>

- 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

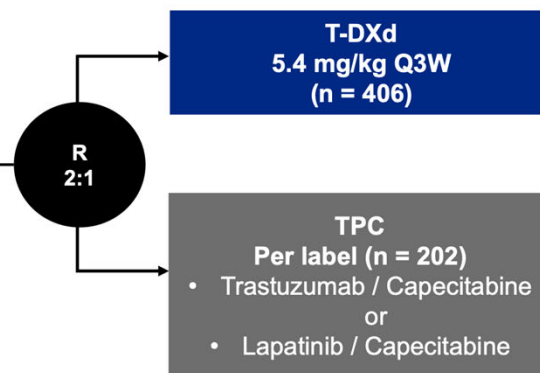
## Stratification factors

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

Majority with 2-3 lines of prior therapy

At data cutoff (June 30, 2022), the median duration of follow-up<sup>d</sup> was:

- 21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- 18.6 months** (range, 0-45.7 months) in the TPC arm



## Primary endpoint

- PFS (BICR<sup>b</sup>)

## Key secondary endpoint

- OS

## Secondary endpoints

- ORR (BICR<sup>b</sup>)
- DoR (BICR<sup>b</sup>)
- PFS (investigator)
- Safety

## Exploratory endpoints

- CBR (BICR<sup>b</sup>)
- PFS2<sup>c</sup> (investigator)

## Protocol-prespecified statistical analysis plan

- Primary analysis planned for ~372 BICR PFS events observed or 18 months from the last patient randomized, whichever came first
- Group sequential testing was used to compare OS between treatment groups hierarchically, provided PFS was significant

## PFS

### Median (95% CI), months

T-DXd	TPC
17.8 (14.3-20.8)	6.9 (5.5-8.4)
HR (95% CI): 0.3589 (0.2840-0.4535)	
<i>P</i> < 0.000001	

## OS

### Median (95% CI), months

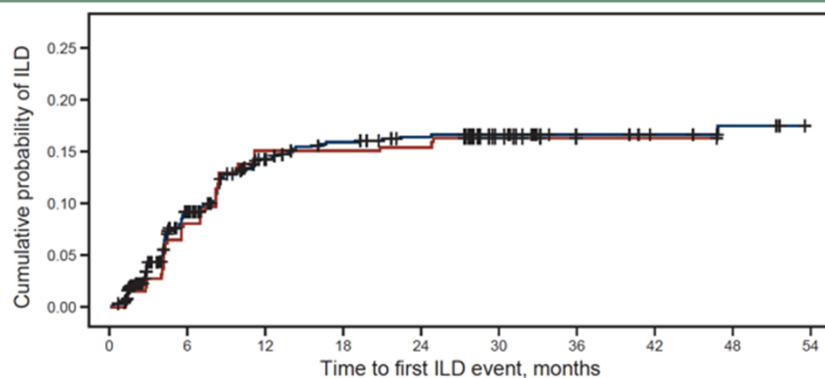
T-DXd	TPC
39.2 (32.7-NE)	26.5 (21.0-NE)
HR (95% CI): 0.6575 (0.5023-0.8605)	
<i>P</i> = 0.0021 <sup>a</sup>	

## Toxicity

- ILD 10.4% (0.5% gr 5)
- Nausea 72.5%
- Alopecia 37.1%

Krop et al, SABCS 2022

## Pooled Analysis of ILD/Pneumonitis in 9 Trastuzumab Deruxtecan Monotherapy Studies



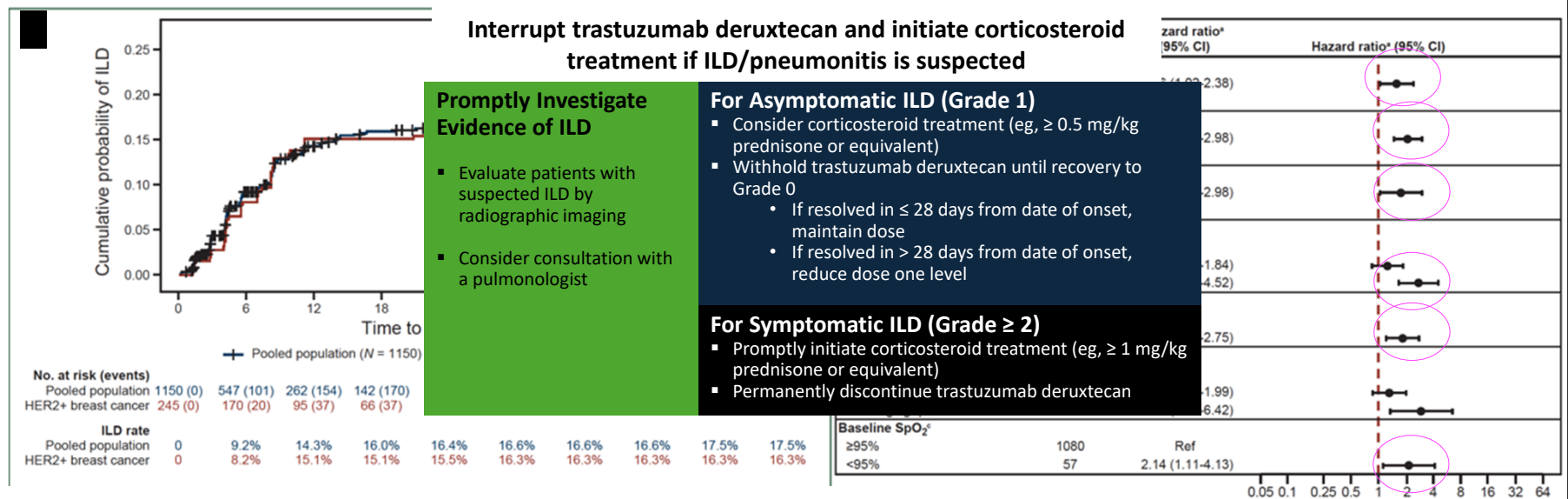
<b>No. at risk (events)</b>										
Pooled population	1150 (0)	547 (101)	262 (154)	142 (170)	84 (174)	35 (176)	13 (176)	7 (176)	4 (177)	0 (177)
HER2+ breast cancer	245 (0)	170 (20)	95 (37)	66 (37)	45 (38)	11 (40)	2 (40)	1 (40)	0 (40)	0 (40)
<b>ILD rate</b>										
Pooled population	0	9.2%	14.3%	16.0%	16.4%	16.6%	16.6%	16.6%	17.5%	17.5%
HER2+ breast cancer	0	8.2%	15.1%	15.1%	15.5%	16.3%	16.3%	16.3%	16.3%	16.3%

Potential risk factor	Patients, n (N = 1150)	Hazard ratio* (95% CI)	Hazard ratio* (95% CI)
<b>Age group</b>			
<65 years	754	1.56 (1.02-2.38)	
≥65 years	396	Ref	
<b>Country</b>			
Japan	506	2.08 (1.45-2.98)	
Non-Japan	644	Ref	
<b>Lung comorbidities<sup>b</sup></b>			
Yes	81	1.75 (1.03-2.98)	
No	1069	Ref	
<b>Baseline renal function<sup>c,d</sup></b>			
Normal	470	Ref	
Mild decrease	458	1.24 (0.83-1.84)	
Moderate/severe decrease	196	2.73 (1.65-4.52)	
<b>Time since disease diagnosis<sup>e</sup></b>			
0 to ≤4 years	624	Ref	
>4 years	403	1.82 (1.20-2.75)	
<b>Dose</b>			
5.4 mg/kg q3w	315	Ref	
6.4 mg/kg q3w	808	1.30 (0.85-1.99)	
>6.4 mg/kg q3w	27	2.92 (1.32-6.42)	
<b>Baseline SpO<sub>2</sub><sup>f</sup></b>			
≥95%	1080	Ref	
<95%	57	2.14 (1.11-4.13)	

- 1150 pts (44.3% breast cancer) with a median treatment duration 5.8 mo (0.7-56.3)
- Overall incidence: 15.4% (grade 5: 2.2%); grade 1-2: 77.4%
- 87% had their first event within 12 months of their first dose

Powell et al, ESMO Open 2022

## Pooled Analysis of ILD/Pneumonitis in 9 Trastuzumab Deruxtecan Monotherapy Studies

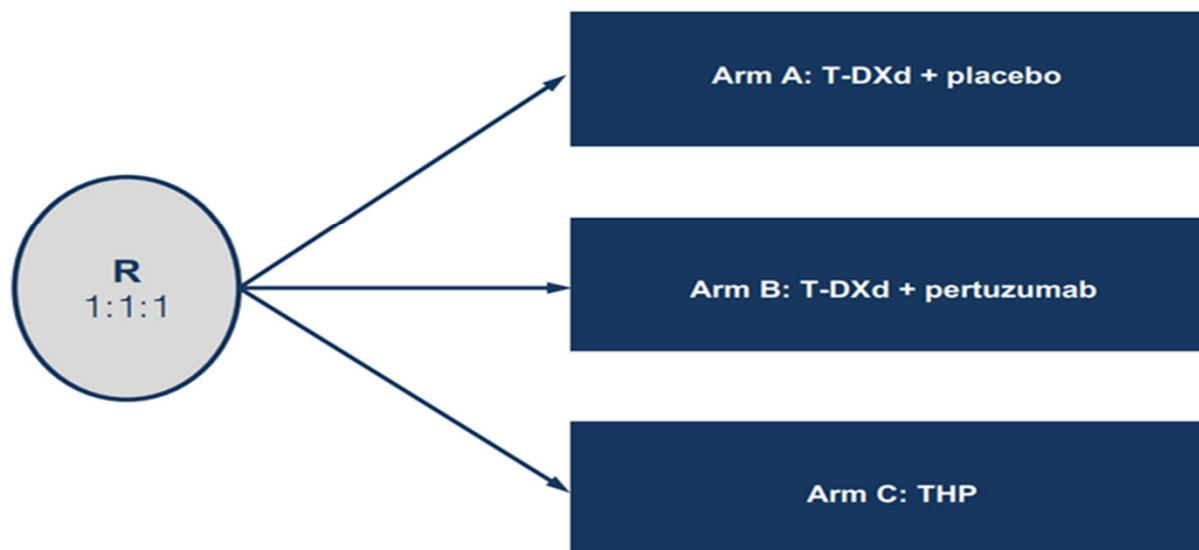


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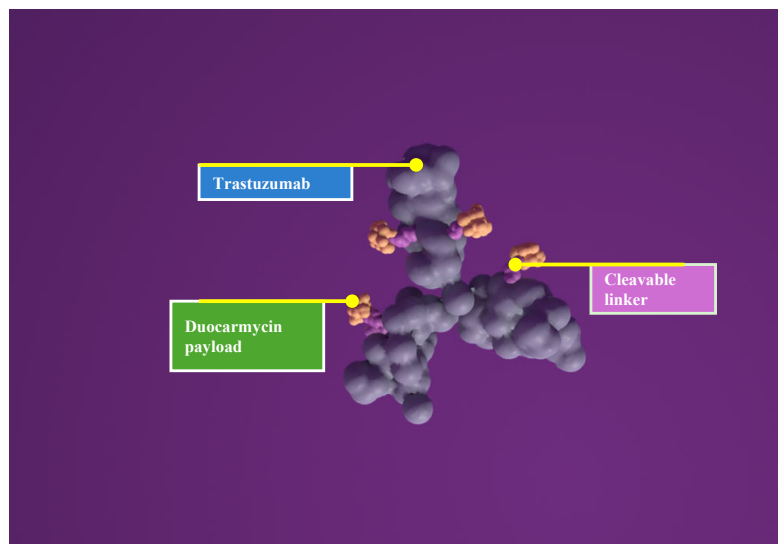
Powell et al, ESMO Open 2022

## T-DXd as first line therapy?

DESTINY-Breast09: A Phase 3 Trial of T-DXd Alone or in Combination With Pertuzumab in First-Line HER2+ MBC



## Trastuzumab Duocarmazine (SYD985)<sup>1,2</sup>



- HER2-targeting ADC<sup>1</sup>
- Duocarmycins are DNA-alkylating agents composed of a DNA-alkylating and a DNA-binding moiety<sup>2</sup>

1. Banerji U et al. *Lancet Oncol.* 2019;20(8):1124-1135; 2. Rinnerthaler G et al. *Int J Mol Sci.* 2019;20(5):1115.

## Clinical Trial Design (TULIP)

## New Antibody-Drug Conjugates Trastuzumab-Duocarmazine

Patients with HER2+, unresectable, locally advanced and/or metastatic BC; progression on or after ≥ 2 HER2-targeted regimens or after T-DM1; ECOG PS 0-2 (Planned N = 345)

Trastuzumab Duocarmazine Q3W (planned n = 230)

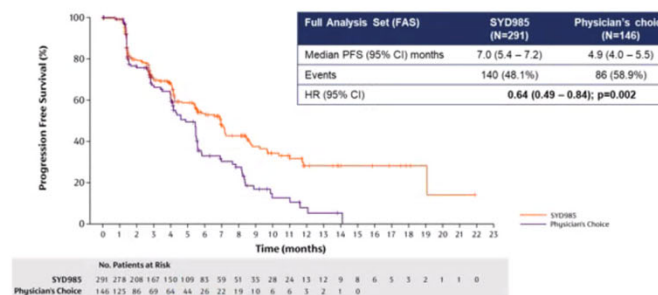
Physician's Choice: Lapatinib/Capecitabine, Trastuzumab/Capecitabine, Trastuzumab/Vinorelbine, Trastuzumab/Eribulin (planned n = 115)

ORR

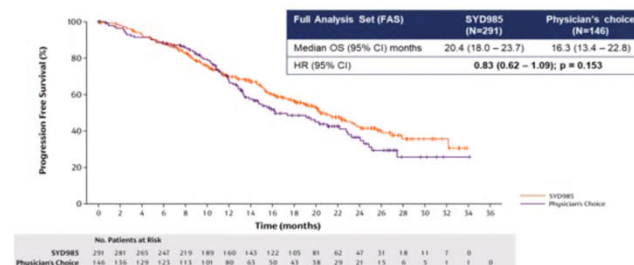
Number of patients with	SYD985 (N=291)	Physician's choice (N=146)
Measurable disease at baseline	252 (86.6%)	122 (83.6%)
Overall Response Rate <sup>#</sup> (PR or CR)	70 (27.8%)	36 (29.5%)
Reduction Target lesion measurement <sup>#</sup>	177 (70.2%)	71 (58.2%)
Clinical Benefit Rate	112 (38.5%)	47 (32.2%)

<sup>#</sup>pts with measurable disease used as denominator

PFS



OS



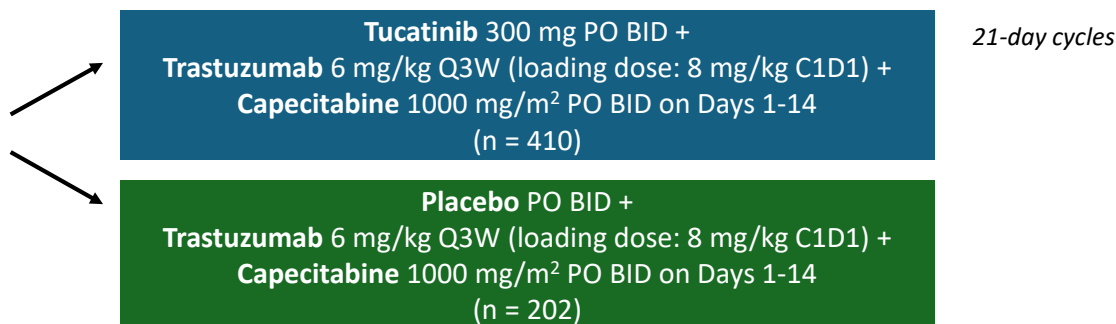
Saura C, et al. ESMO 2021

## HER2CLIMB: Tucatinib + Trastuzumab + Capecitabine in Previously Treated HER2+ MBC

- Randomized, double-blind, placebo-controlled, active comparator phase II trial

**Patients with HER2+ MBC;  
prior trastuzumab,  
pertuzumab, and T-DM1; ECOG  
PS 0/1;  
brain mets allowed\*  
(N = 612)**

\*Including previously treated stable mets, untreated mets not needing immediate local therapy, and previously treated progressing mets not needing immediate local therapy.



- Primary endpoint: PFS (RECIST v 1.1 by BICR) among first 480 randomized patients
- Secondary endpoints (total population): OS, PFS in patients with brain mets, ORR in patients with measurable disease, safety in patients who received  $\geq 1$  dose of study tx

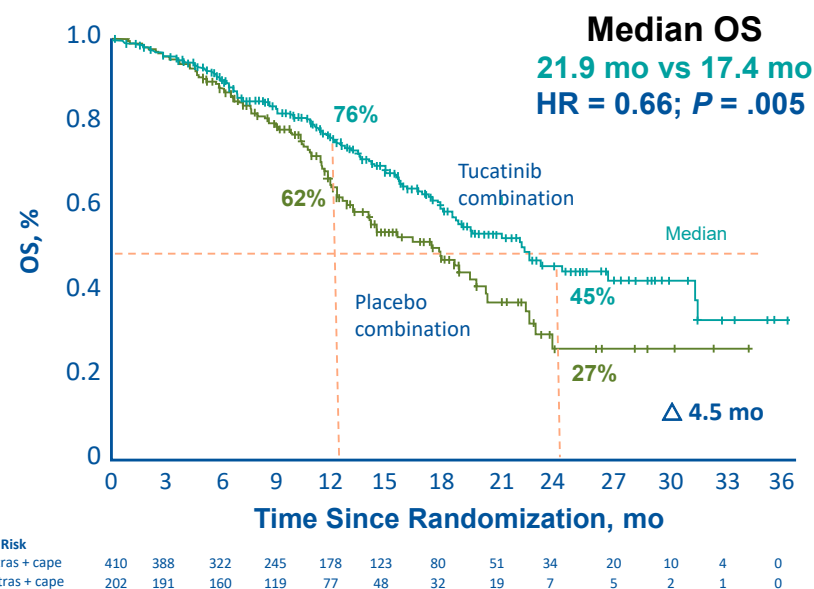
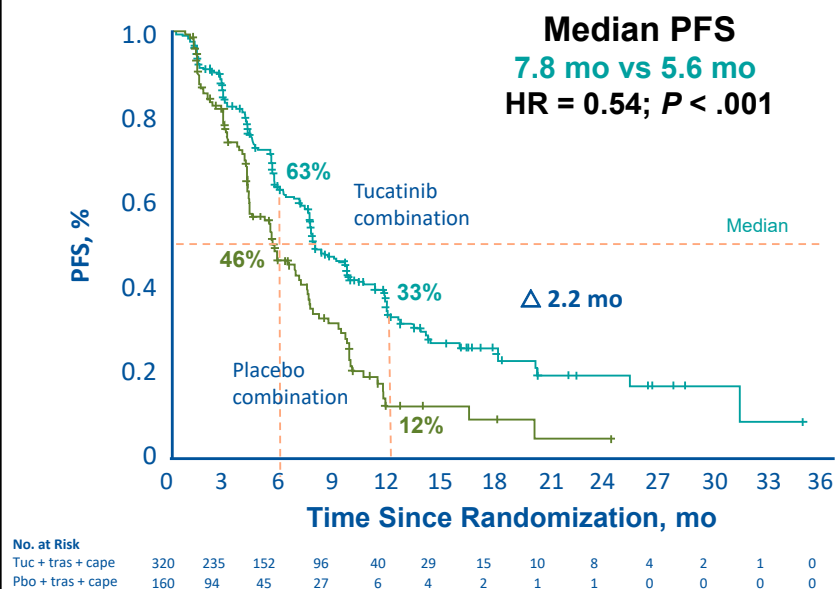
Murthy. NEJM. 2020; 382:597.



# HER2CLIMB: Randomized Phase 2 Trial of Tucatinib<sup>1</sup>

Tucatinib + Capecitabine + Trastuzumab vs Capecitabine + Trastuzumab

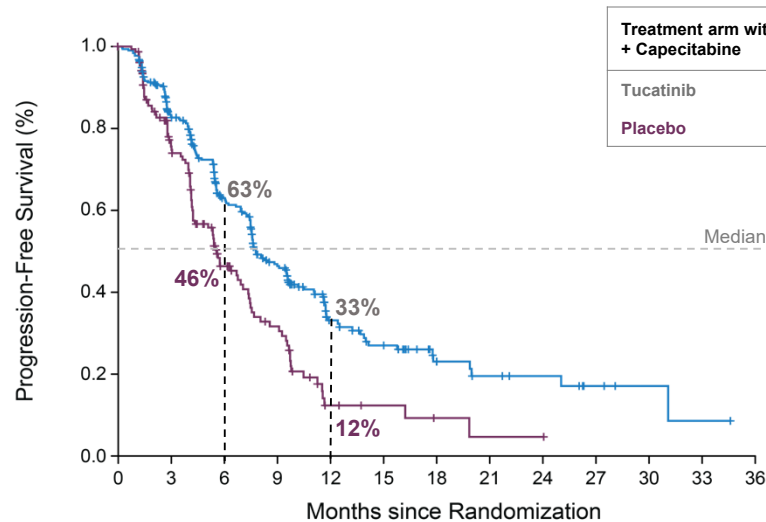
*Tucatinib Improves PFS and OS*



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1 poster abstracts, 10 oral presentations

# Progression-Free Survival with Tucatinib Added to Capecitabine and Trastuzumab in HER2+ MBC (Including with Brain Metastases): HER2CLIMB Study Results



No. at Risk												
TUC+Tras+Cape 320	235	152	98	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

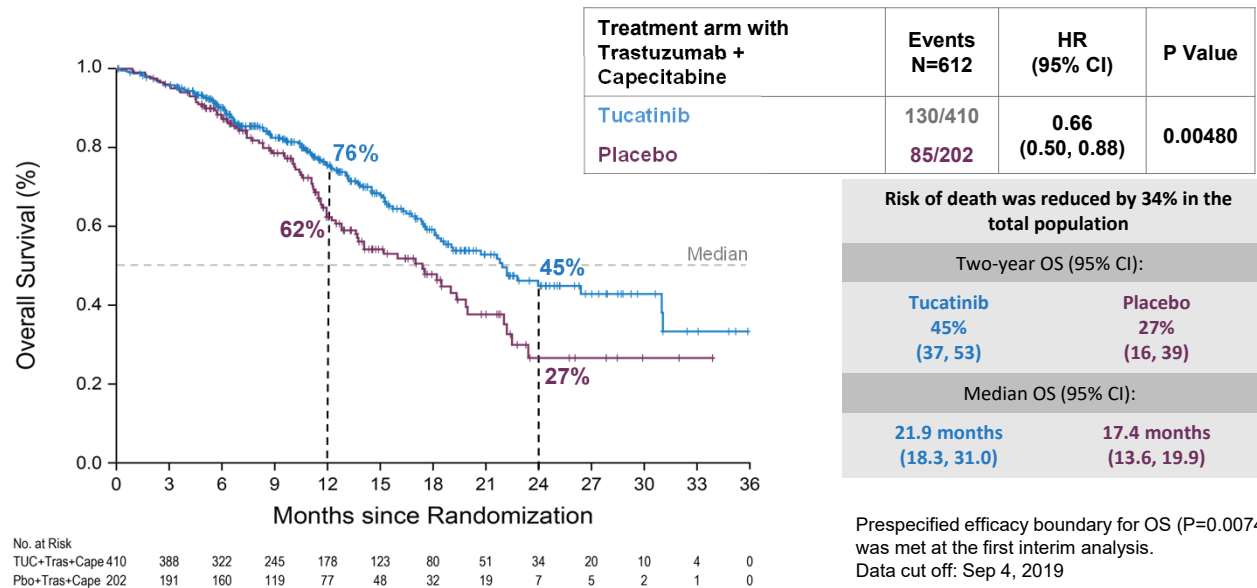
Treatment arm with Trastuzumab + Capecitabine	Events, N=480	HR (95% CI)	P Value
Tucatinib	178/320	0.54 (0.42, 0.71)	<0.00001
Placebo	97/160		

Risk of progression or death was reduced by 46% in the primary endpoint population	
One-year PFS (95% CI):	
<b>Tucatinib</b>	<b>Placebo</b>
33% (27, 40)	12% (6, 21)
Median PFS (95% CI):	
<b>7.8 months (7.5, 9.6)</b>	<b>5.6 months (4.2, 7.1)</b>

Prespecified efficacy boundary for PFS: P=0.05  
Data cut off: Sep 4, 2019

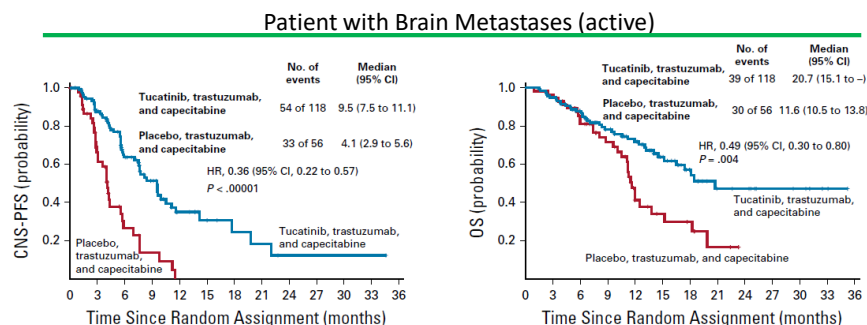
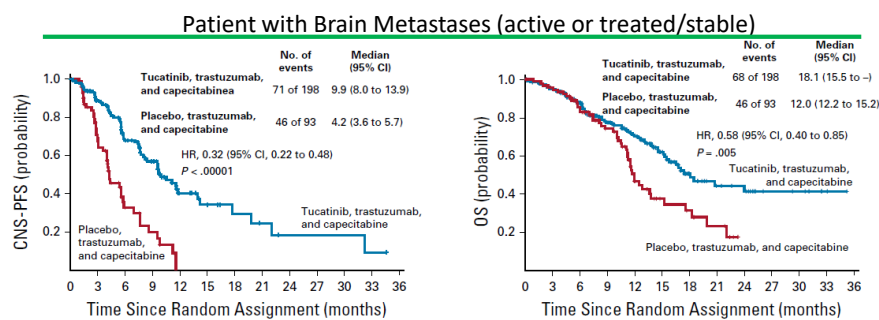
Murthy R, et al. *N Engl J Med.* 2020;382(7):597-609.

# Overall Survival with Tucatinib Added to Capecitabine and Trastuzumab in HER2+ MBC (Including with Brain Metastases): HER2CLIMB Study Results



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

## Intracranial CNS-Specific Outcomes: HER2CLIMB Study Results

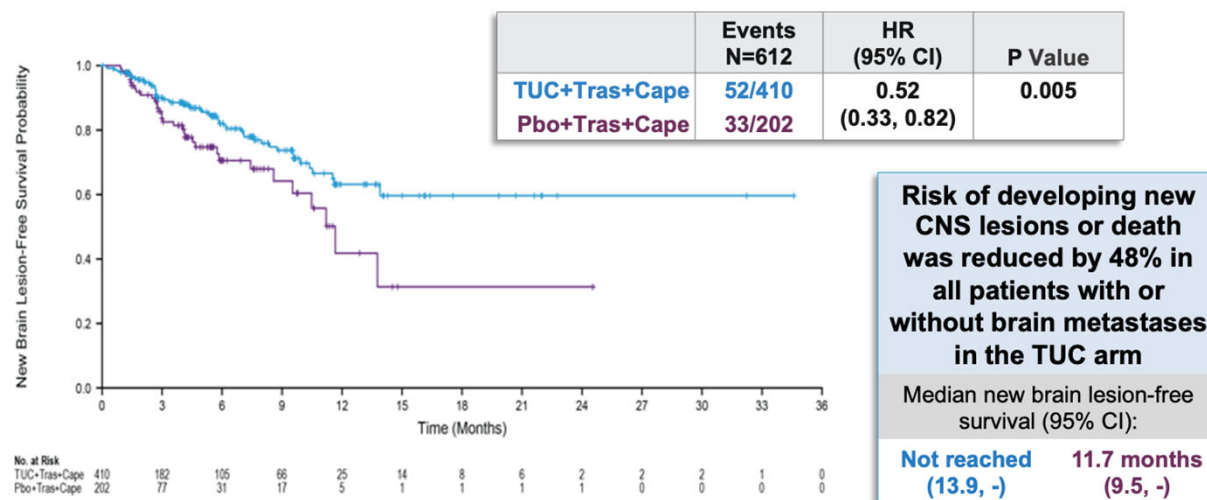


Intra-Cranial CNS Response (RECIST) N=75	Tucatinib N=55 N (%)	Placebo N=20 N (%)
CR	3 (5.5)	1 (5.0)
PR	23 (41.8)	3 (15.0)
SD	24 (43.6)	16 (80.0)
PD	2 (3.6)	0
Not Available	3 (5.5)	0
Confirmed ORR	26 (47.3)	4 (20.0)
95% CI	33.7-61.2%	5.7-43.7%
Stratified p-value	0.03	
DOR (months)	6.8	3.0

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; ORR=objective response rate (CR+PR); DOR=duration of intracranial response

Lin NU, et al. *J Clin Oncol*. 2020;38(23):2610-2619.

## Time to New Brain Lesions or Death in All HER2CLIMB Patients



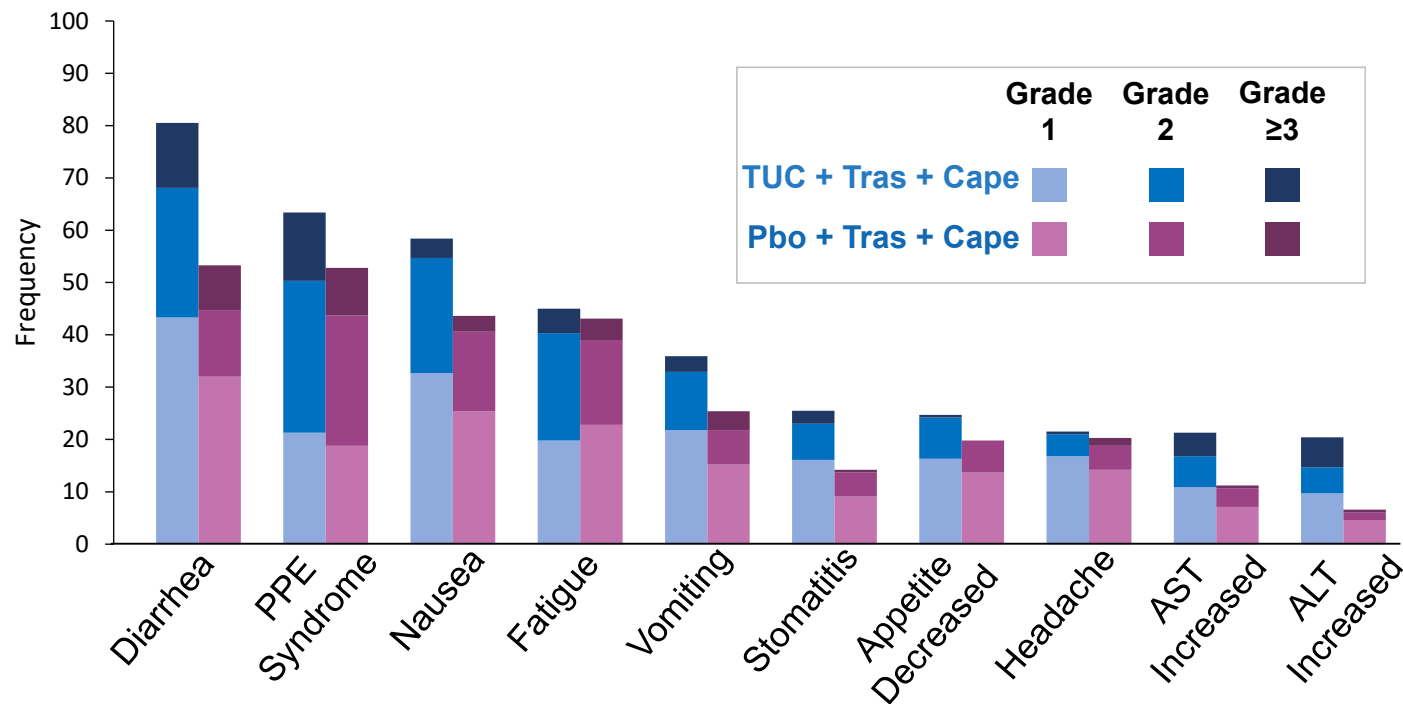
- Time to new brain lesion-free survival was defined as time from randomization to new lesion in the brain or death by investigator assessment.

Lin NU, et al. Society for NeuroOncology Oral Presentation.

## HER2Climb Safety: It's mostly the cape...

Event	Tucatinib-Combination Group (N=404)		Placebo-Combination Group (N=197)	
	Any Grade	Grade $\geq 3$	Any Grade	Grade $\geq 3$
	<i>number of patients (percent)</i>			
Any adverse event	401 (99.3)	223 (55.2)	191 (97.0)	96 (48.7)
Diarrhea	327 (80.9)	52 (12.9)	105 (53.3)	17 (8.6)
PPE syndrome	256 (63.4)	53 (13.1)	104 (52.8)	18 (9.1)
Nausea	236 (58.4)	15 (3.7)	86 (43.7)	6 (3.0)
Fatigue	182 (45.0)	19 (4.7)	85 (43.1)	8 (4.1)
Vomiting	145 (35.9)	12 (3.0)	50 (25.4)	7 (3.6)
Stomatitis	103 (25.5)	10 (2.5)	28 (14.2)	1 (0.5)
Decreased appetite	100 (24.8)	2 (0.5)	39 (19.8)	0
Headache	87 (21.5)	2 (0.5)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	86 (21.3)	18 (4.5)	22 (11.2)	1 (0.5)
Alanine aminotransferase increased	81 (20.0)	22 (5.4)	13 (6.6)	1 (0.5)

## HER2CLIMB: Common Adverse Events (≥20% in the Tucatinib Arm)



PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

Curigliano G, et al. ESMO Breast 2020. Abstract 1370.

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# HER2CLIMB-02 Study Design

- HER2+ LA/MBC with progression after trastuzumab and taxane in any setting<sup>a</sup>
- 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)

## Tucatinib (TUC) + T-DM1

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

## Placebo (PBO) + T-DM1

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

## 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.  
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.<sup>b</sup>

Hurvitz S, et al. SABCS2023

NCT03975647. <https://www.clinicaltrials.gov/study/NCT03975647>. Accessed Oct 5, 2023. Date of data cutoff: Jun 29, 2023. Patients were enrolled from Oct 8, 2019, to Jun 16, 2022.

<sup>a</sup> Patients who received prior tucatinib, afatinib, T-DXd, or any investigational anti-HER2, anti-EGFR, or HER2 TKIs were not eligible. Patients who received lapatinib and neratinib were ineligible if the drugs were received within 12 months of starting study treatment, and patients who received pyrotinib for recurrent or metastatic breast cancer were not eligible. These patients were eligible if the drugs were given for ≤21 days and were discontinued for reasons other than disease progression or severe toxicity.

<sup>b</sup> Subsequent OS analyses are planned upon 80% and 100% of events. 1L, first-line; BID, twice daily; cORR, confirmed objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; LA/MBC, locally advanced or metastatic breast cancer; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, orally; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKIs, tyrosine kinase inhibitors; TUC, tucatinib.

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## HER2CLIMB-02: Demographics and Baseline Characteristics

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

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

Hurvitz S, et al. SABCS 2023

<sup>a</sup> Includes 2 patients with missing brain metastases data.  
<sup>b</sup> Five patients in TUC + T-DM1 arm and 7 patients in PBO + T-DM1 arm had unknown stage.  
 ECOG, Eastern Cooperative Oncology Group; PBO, placebo; T-DM1, trastuzumab emtansine; TUC, tucatinib.  
 Date of data cutoff: Jun 29, 2023.

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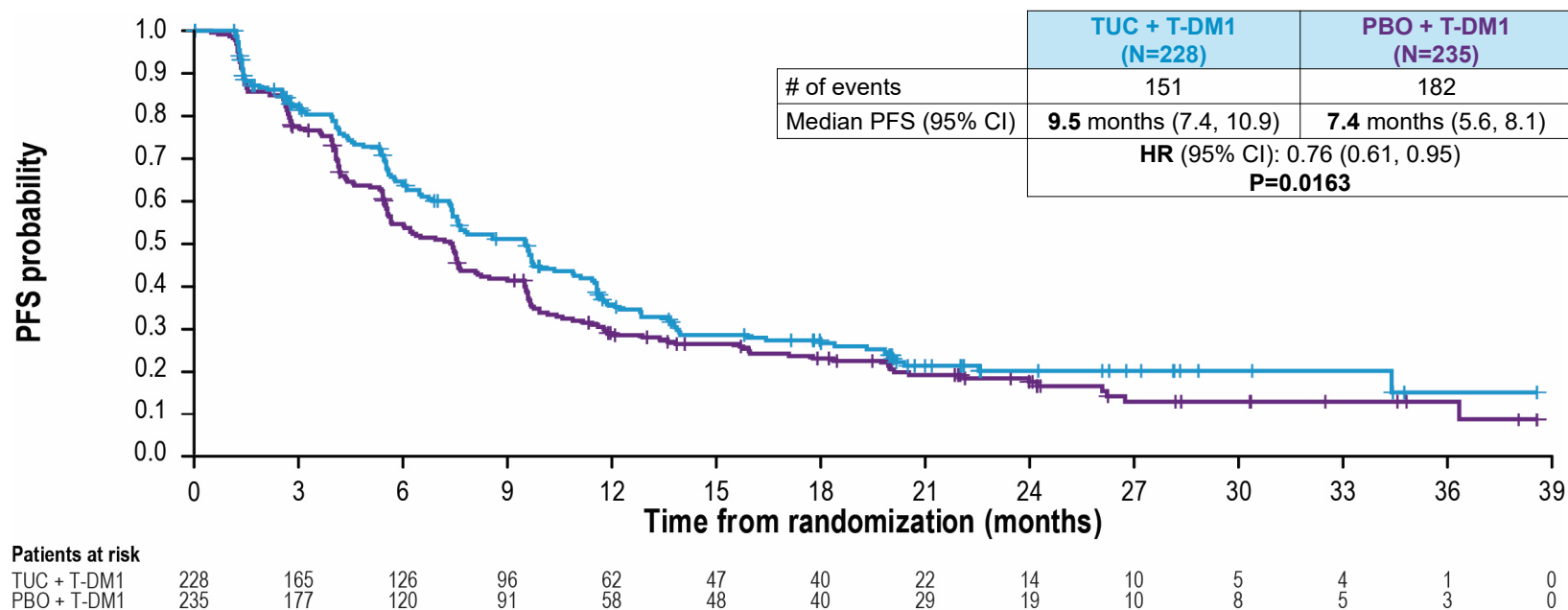
## HER2CLIMB-02: Prior Systemic Therapies

	TUC + T-DM1 (N=228)	PBO + T-DM1 (N=235)
<b>Median prior lines of systemic therapy in metastatic setting (range)</b>	1 (0-8)	1 (0-6)
<b>Prior lines of systemic therapy in metastatic setting, n (%)</b>		
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)
<b>Received prior pertuzumab treatment, n (%)</b>	202 (88.6)	214 (91.1)
<b>Received prior anti-HER2 TKIs, n (%)</b>	3 (1.3)	5 (2.1)

Hurvitz S, et al. SABCS 2023

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# HER2CLIMB-02: Progression-Free Survival

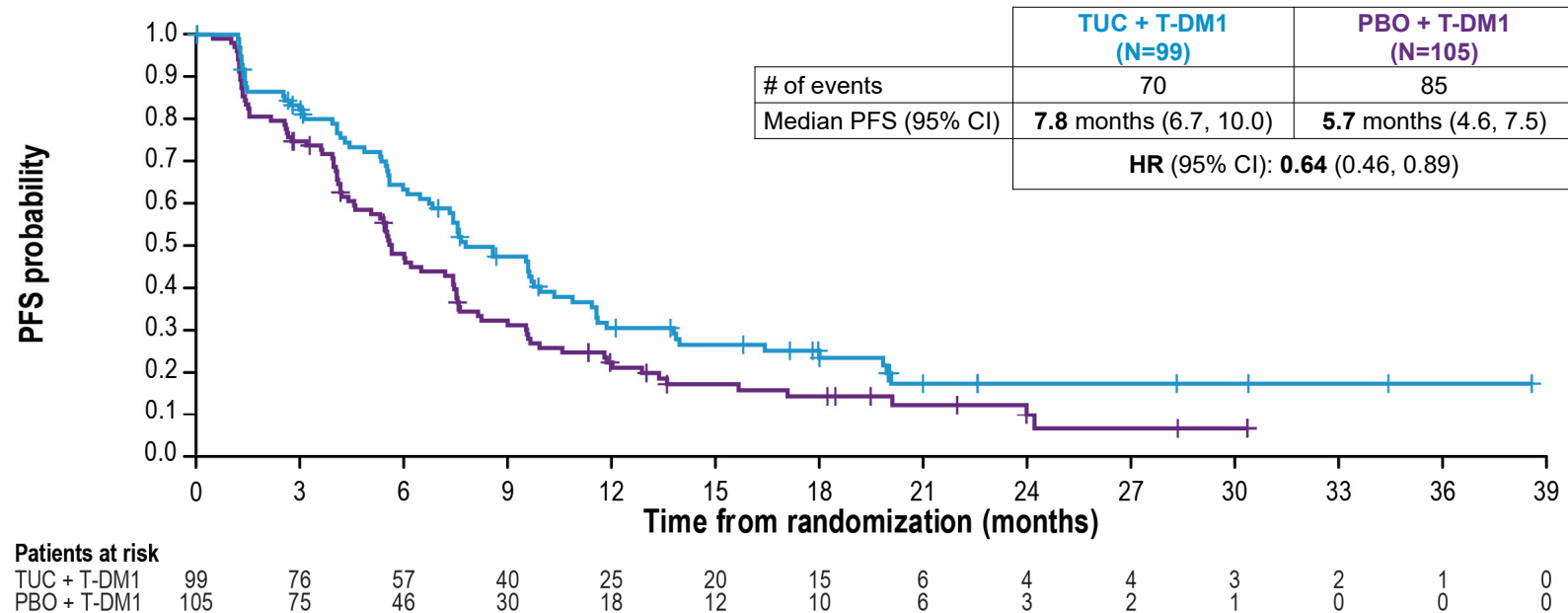


HR, hazard ratio; PBO, placebo; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TUC, tucatinib.  
Date of data cutoff: Jun 29, 2023.

Hurvitz S, et al. SABCS 2023

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# HER2CLIMB-02: PFS in Patients with Brain Metastases<sup>a</sup>

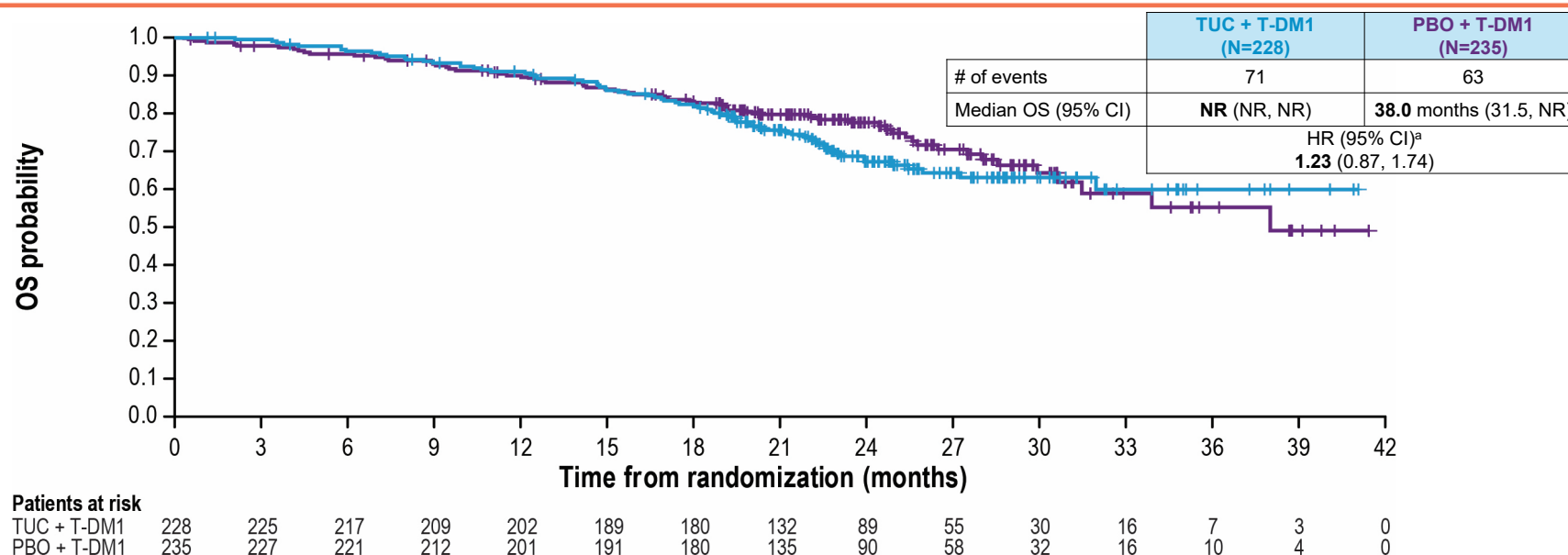


Hurvitz S, et al. SABCS 2023

<sup>a</sup> The outcome was not formally tested.  
 HR, hazard ratio; PBO, placebo; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TUC, tucatinib.  
 Date of data cutoff: Jun 29, 2023.

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# HER2CLIMB-02: Overall Survival



Median follow-up was 24.4 months. As of data cutoff, 134 out of 253 (53%) prespecified events for the OS final analysis were observed. Interim OS results did not meet the prespecified crossing boundary of  $P=0.0041$ .

<sup>a</sup> The proportional hazard assumption was not maintained post-18 months, with heavy censoring on both arms. HRs, hazard ratios; NR, not reached; OS, overall survival; PBO, placebo; T-DM1, trastuzumab emtansine; TUC, tucatinib. Date of data cutoff: Jun 29, 2023.

Hurvitz S, et al. SABCS 2023

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# HER2CLIMB-02: Adverse Events of Interest

## Hepatic TEAEs

- Grade ≥3 hepatic TEAEs greater in TUC + T-DM1 arm (28.6% vs 7.3%), primarily due to AST/ALT elevations
- No Hy's law cases were identified
- 85% of all-grade hepatic TEAEs in TUC + T-DM1 arm resolved or returned to grade 1, with median of 22 days to resolution<sup>a</sup>

### Dose modifications Due to Hepatic TEAEs

	TUC + T-DM1 (N=231) n (%)	PBO + T-DM1 (N=233) n (%)
TUC/PBO dose holds	76 (32.9)	26 (11.2)
TUC/PBO dose reductions	46 (19.9)	12 (5.2)
<b>Treatment discontinuation</b>		
TUC/PBO	16 (6.9)	5 (2.1)
T-DM1	18 (7.8)	5 (2.1)

## Diarrhea

- Grade ≥3 events reported in 4.8% of TUC + T-DM1 arm and 0.9% of PBO + T-DM1 arm

### Dose modifications Due to Diarrhea

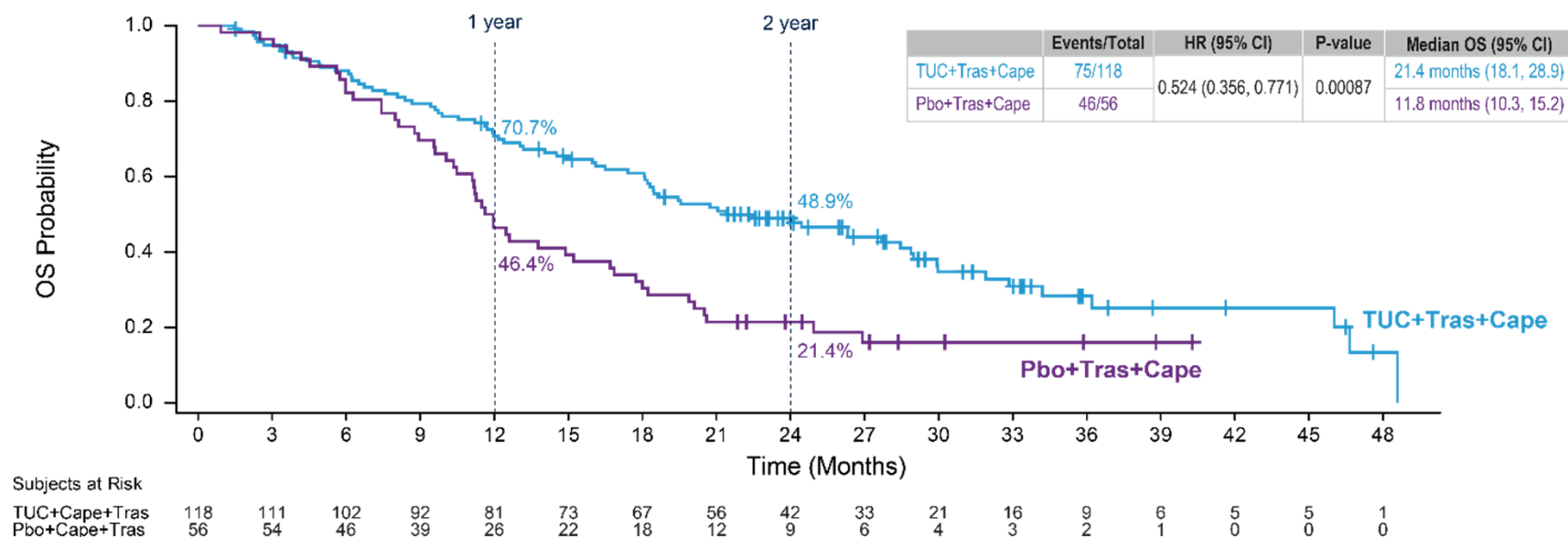
	TUC + T-DM1 (N=231) n (%)	PBO + T-DM1 (N=233) n (%)
TUC/PBO dose holds	9 (3.9)	2 (0.9)
TUC/PBO dose reductions	9 (3.9)	1 (0.4)
<b>Treatment discontinuation</b>		
TUC/PBO	1 (0.4)	0
T-DM1	0	0

<sup>a</sup> For PBO + T-DM1 arm, 75% of all-grade hepatic TEAEs resolved or returned to grade 1, with median of 22 days to resolution. ALT, alanine aminotransferase; AST, aspartate aminotransferase; PBO, placebo; T-DM1, trastuzumab emtansine; TEAEs, treatment-emergent adverse events; TUC, tucatinib. Date of data cutoff: Jun 29, 2023.

Hurvitz S, et al. SABCS 2023

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# HER2CLIMB: OS for Patients With Active Brain Metastases



Median OS was 9.6 months longer in the tucatinib arm compared with the control arm in patients with active brain metastases.

Lin NU, et al. SABCS 2021. Abstract PD4-04.

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# The NEW ENGLAND JOURNAL of MEDICINE

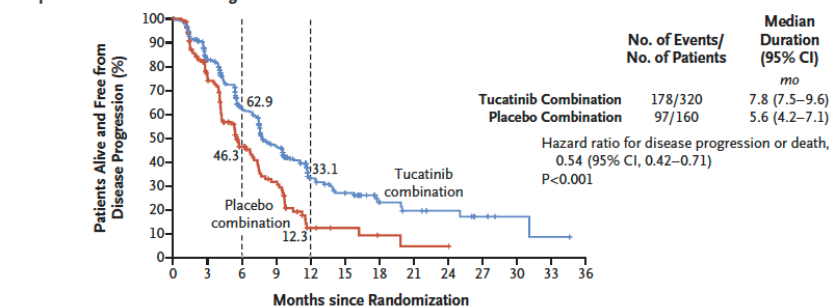
ESTABLISHED IN 1812

FEBRUARY 13, 2020

VOL. 382 NO. 7

## Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

A Kaplan-Meier Estimates of Progression-free Survival

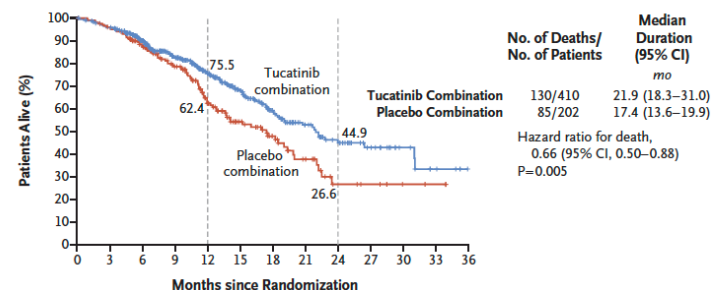


### No. at Risk

Tucatinib combination	320	235	152	98	40	29	15	10	8	4	2	1	0
Placebo combination	160	94	45	27	6	4	2	1	1	0	0	0	0

## Results HER2climb-02 How to incorporate?

A Kaplan-Meier Estimates of Overall Survival



### No. at Risk

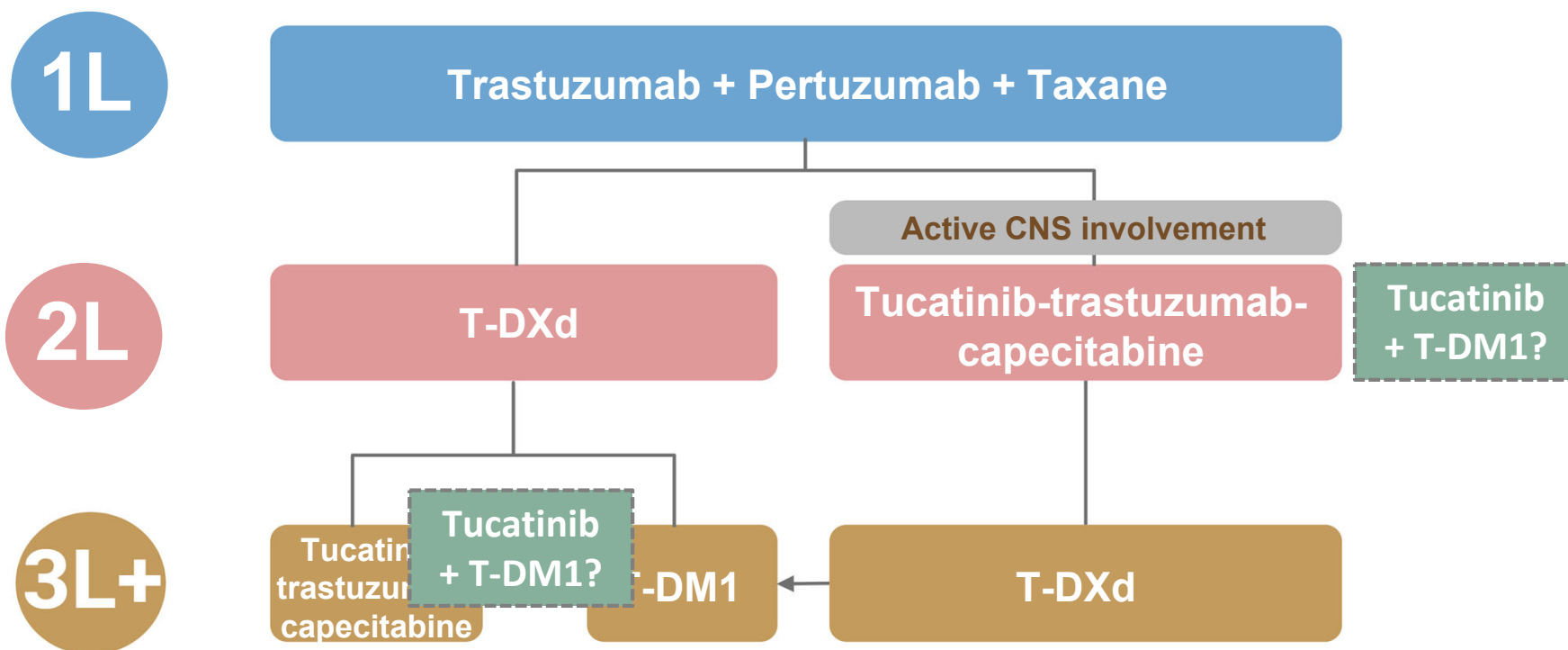
Tucatinib combination	410	388	322	245	178	123	80	51	34	20	10	4	0
Placebo combination	202	191	160	119	77	48	32	19	7	5	2	1	0

100% prior pertuzumab, trastuzumab and T-DM1

Active untreated brain metastases was eligible, including those >2cm

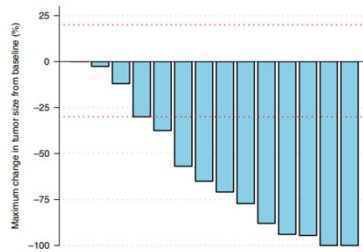


## Current algorithm: where will HER2CLIMB-02 fit in?



# Trastuzumab Deruxtecan in pts with active brain mets

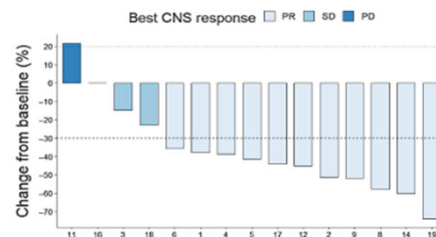
**TUXEDO-1 study (n=15)**



Intracranial RR = 73.3%

**DFCI/MDACC/Duke (n=15\*)**

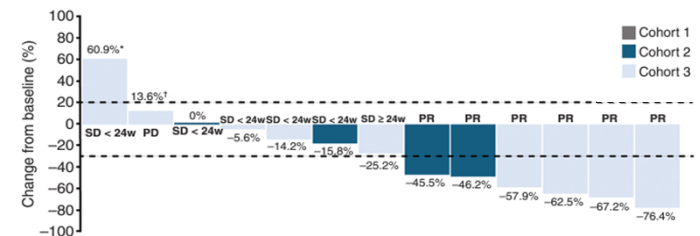
\*15/17 with evaluable intracranial RR



Intracranial RR = 73%

**DEBBRAH (n=13\*)**

\*active BM cohorts (2 and 3)



Overall intracranial RR = 46.2%  
(asymptomatic untreated + progressing BMs)



## A Pooled Analysis of Trastuzumab Deruxtecan in Patients With HER2-Positive Metastatic Breast Cancer With Brain Metastases (BMs) from DESTINY-Breast01, -02, and -03

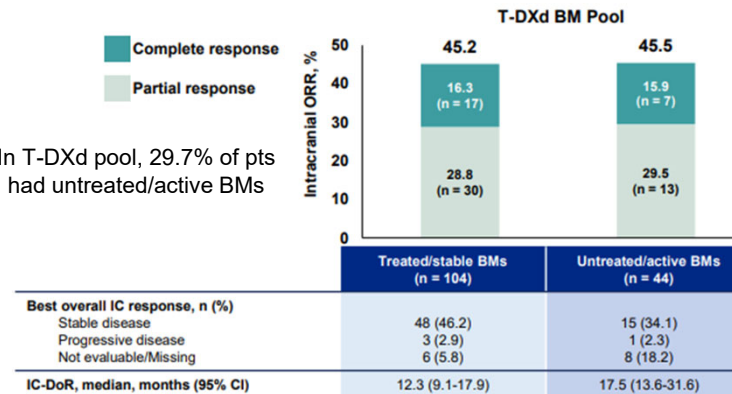
Presentation 3770

Sara A. Hurvitz<sup>1</sup>, Shanu Modi, Wei Li, Yeon Hee Park, Wei-Pang Chung, Sung-Bae Kim, Javier Cortes, Toshinari Yamashita, Jose Luiz Pedrini, Seock-Ah Im, Ling-Ming Tseng, Nadia Harbeck, Ian Krop, Giuseppe Curigliano, Elton Mathias, Jillian Cathcart, Antonio Cagnazzo, Shahid Ashfaq, Anton Egorov, Fabrice André

On behalf of the DESTINY-Breast01, -02, and -03 pooled investigators

Complete response  
Partial response

In T-DXd pool, 29.7% of pts had untreated/active BMs



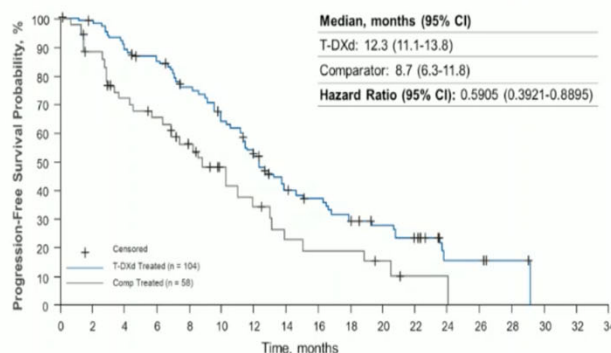
Bartsch R et al, Nature Medicine 2022; Kabraji S et al, CCR 2023; Pérez-García JM et al, Neuro-Oncology 2023; Hurvitz S et al, ESMO 2023



DESTINY-Breast01, -02, and -03

## Exploratory CNS-PFS per BICR

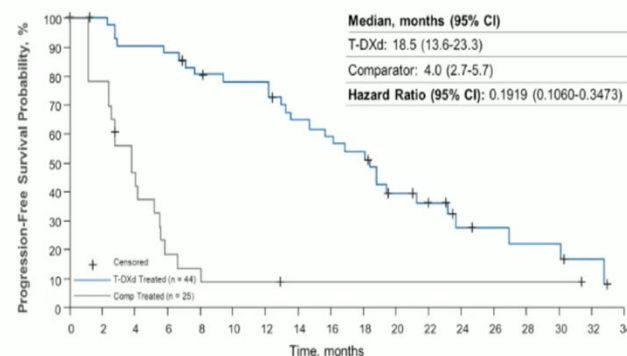
### Treated/Stable BMs



Patients still at risk

T-DXd Treated (n = 104)	104	100	89	83	72	58	46	32	28	21	18	12	4	4	2	0	0	0
Comparator Treated (n = 58)	58	44	33	29	22	14	10	6	5	5	3	1	0	0	0	0	0	0

### Untreated/Active BMs



Patients still at risk

T-DXd Treated (n = 44)	44	41	37	36	32	30	30	24	22	20	13	11	6	5	4	4	2	0
Comparator Treated (n = 25)	25	18	11	5	3	2	2	1	1	1	1	1	1	1	1	1	0	0

- T-DXd demonstrated a trend towards prolonged CNS-PFS over comparator, with a noticeably greater advantage for patients with untreated/active BMs

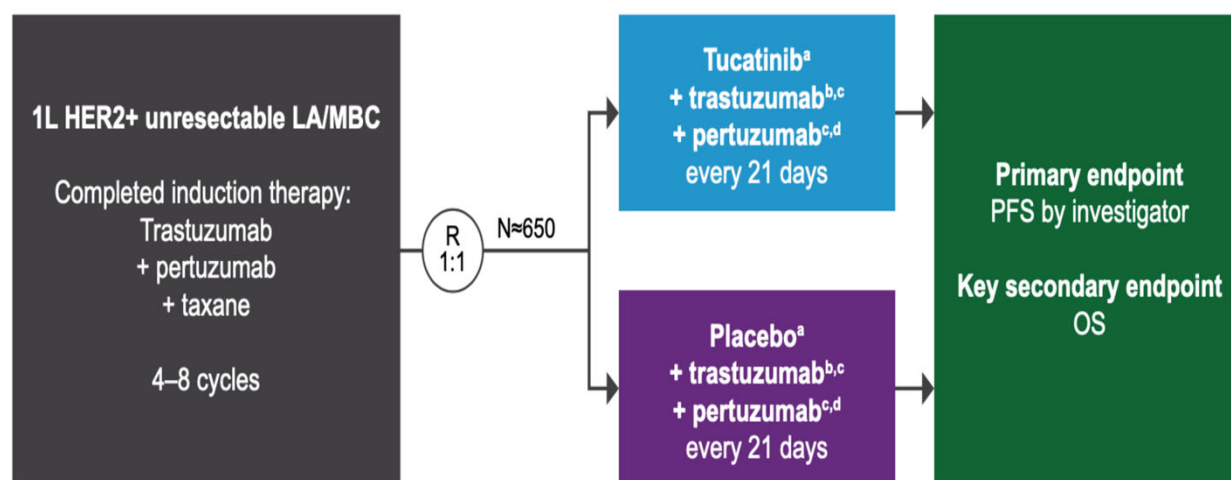
BICR, blinded independent central review; BM, brain metastasis; CNS, central-nervous system; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.  
CNS-PFS was defined by BICR as only radiological progression.



Sara A. Hurvitz, MD

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# HER2CLIMB-05



HER2CLIMB-05 (NCT05132582) is a phase 3, randomized, double-blind study evaluating tucatinib or placebo in combination with trastuzumab plus pertuzumab as maintenance therapy in the 1L setting for patients with unresectable LA or metastatic HER2+ breast cancer following SOC induction therapy



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# Brain metastases in metastatic breast cancer: prevalence per line of treatment and cumulative incidence in a cohort of 18075 real-world patients

Sarah L. Sammons, Jose Pablo Leone, Thibaut Sanglier, Peter Lambert, Filippo Montemurro, Raf Poppe, Eleonora Restuccia, Sara M. Tolaney, Nancy U. Lin

Sarah L. Sammons, MD

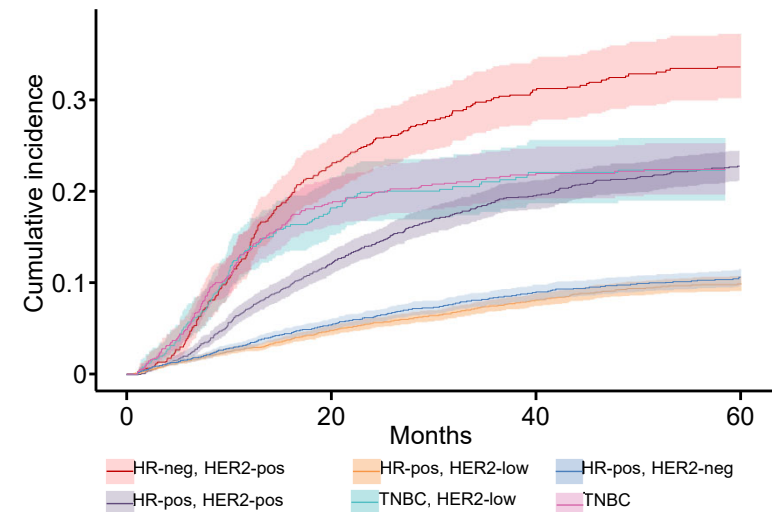
Dana-Farber Cancer Institute, Boston, MA

# Results

Overall, 18075 patients were included; 1102 (6.1%) had a BM at the index date; CIF was run on the remaining 16973.

Cumulative incidence of BM at 60 months was 23% in HR+/HER2+, 34% HR-/HER2+, 10% in HR+/HER2-, and 22% in TNBC

Prevalence of BM per line of therapy, %	HR-pos, HER2-pos (1L N=3062)	HR-neg, HER2-pos (1L N=902)	HR-pos, HER2-neg [HER2-low] (1L N=12331) [1L n=7062]	TNBC [HER2-low] (1L N=1780) [1L n=725]
1	6.3	11.2	2.7 [2.8]	11.1 [12.1]
2	17.6	31.2	5.2 [5.8]	17.5 [17.3]
3	21.5	36.3	6.7 [7.4]	21.5 [20.8]
4	26.1	37.1	8.5 [9.4]	26.1 [27.9]
5+	26.5	36.9	9.7 [10.5]	29.1 [25.7]



BM, brain metastasis; CIF, cumulative incidence function; HR, hormone receptor; mBC, metastatic breast cancer; pts, patients; TNBC, triple-negative breast cancer.



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# Clinical risk factors of Central Nervous System (CNS)-related death in patients with HER2-positive(+) metastatic breast cancer

**Speaker: Emanuela Ferraro, MD**

Breast Medicine Service, Memorial Sloan Kettering Cancer Center, New York, NY

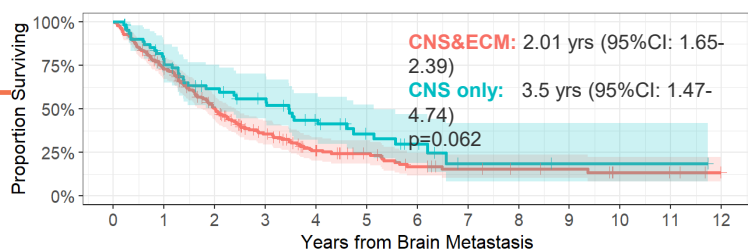
No personal financial disclosure

Study team: **Nelson Moss**, Anne S. Reiner, Andrew D. Seidman, Chau T Dang, Sabrina Zeller, Umberto Tosi, Rabih B Nassif, Samantha Brown and Katherine Panageas

Acknowledgment(s): Terri Brodeur Cancer Foundation (research fellowship 2022-2024); MSKCC Breast Medicine & Neurosurgery Services




**Full cohort Median OS: 2.10 years (95%CI: 1.86-2.50)**

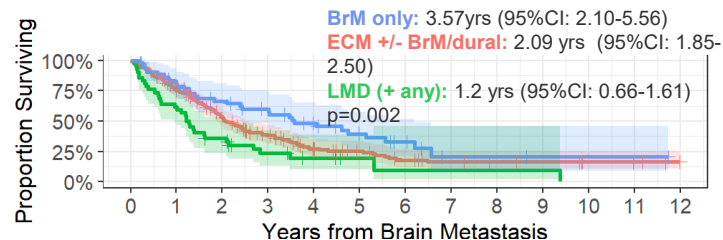





ECM at CNS-disease Dx

At Risk	209	149	97	58	34	24	15	11	9	8	4	3	0
Events	0	56	100	127	141	143	150	151	151	151	152	152	152

 CNS-disease only

At Risk	63	47	34	28	19	12	7	2	2	1	1	1	0
Events	0	13	23	26	32	35	37	39	39	39	39	39	39



		At Risk													
  	ECM +/- BrM/DM	176	129	85	53	31	22	14	10	8	7	4	3	0	
	Lepto (+ any)	42	26	14	7	4	2	1	1	1	1	0	0	0	
	BrM only	54	41	32	26	18	12	7	2	2	1	1	1	0	
		Events													
	ECM +/- BrM/DM	0	43	79	102	116	118	124	125	125	125	125	125	125	
	Lepto (+ any)	0	16	27	31	32	32	33	33	33	33	34	34	34	
	BrM only	0	10	17	20	25	28	30	32	32	32	32	32	32	

## Conclusions

- Overall, the majority of deaths in pts with HER2+ MBC and CNS involvement is attributed to CNS causes
- Pts with CNS-only disease trended towards better OS than pts with concomitant or prior ECM
- LMD and treatment with WBRT are identified as clinically meaningful risk factors for CNS-related death

## Implications

- Prioritization of local and systemic strategies are needed based on CNS/EC disease burden
- CNS-only disease is an emerging subgroup of pts (see PO5-16-01\*, Safonov et al.)
- LMD is an urgent unmet need- inclusion in clinical trials should be allowed and encouraged (phase I to III)
- Consider CNS-related death as a CNS- specific endpoint





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# Analysis of HER2 Expression Changes from Breast Primary to Brain Metastases Including HER2 Low and Impact on Overall Survival

**Alyssa M. Pereslete**, Melissa E. Hughes, Alyssa Patterson, Janet Files, Kyleen Nguyen, Lauren Buckley, Ashka Patel, Abigail Moore, Eric P. Winer, Tianyu Li, Sara M. Tolaney, Nancy U. Lin, Sarah L. Sammons

Herbert Wertheim College of Medicine, Miami FL

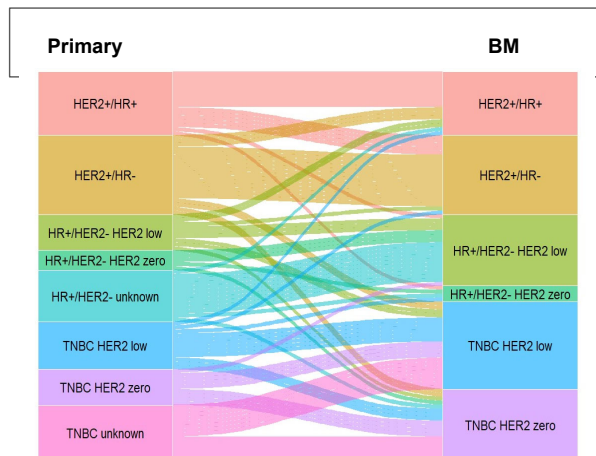
Dana-Farber Cancer Institute, Boston MA

I have the following relevant financial relationships to disclose:

Research support from: 2023 AOA Carolyn L. Kuckein Student Research Fellowship, Breast Cancer Research Foundation, NCI SPORE grant in Breast Cancer to DF/HCC 1P50CA168504

# Subtype between Primary and Metastasis

Clinical subtypes by clinical IHC (n=100)		
	Primary	Brain metastasis
HR+/HER2-	26 (26%)	23 (23%)
HR+/HER2+	17 (17%)	16 (16%)
HER2+/HR-	21 (21%)	20 (20%)
TNBC	35 (35%)	41 (41%)
UNK	3 (3%)	0 (0%)



Of 265 resected brain metastases: **72% were HER2 expressing**  
(57% HER2+ (n=112), 24% HER2-Low (n=48), 19% HER2-0 (n=37).

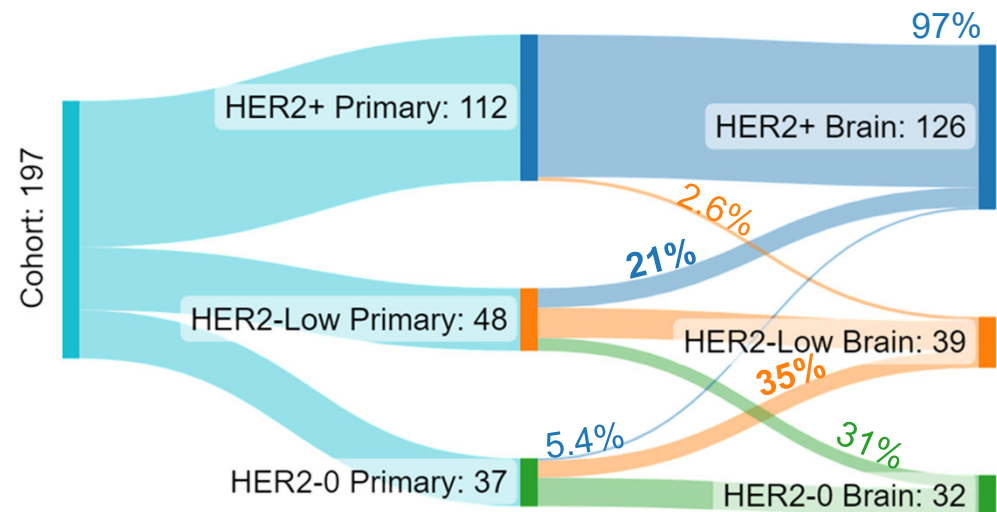


Fig. 2 Subtype Switching From Primary to Brain Metastases (N=197 pairs)

Guadalupe A. Garcia, SABCS2023

Alyssa M. Pereslete , SABCS2023

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# Results

- Patients with HER2+ BMs had a statistically significant lower risk of death at time of follow up vs HER2-Low BMs ( $p = 0.0006$ )
- **Risk of death between patients with HER2-0 and HER2-Low BMs was similar after adjusting for ER and age. ( $p = 0.9$ )**
- Patients with HER2+ BMs have a better prognosis

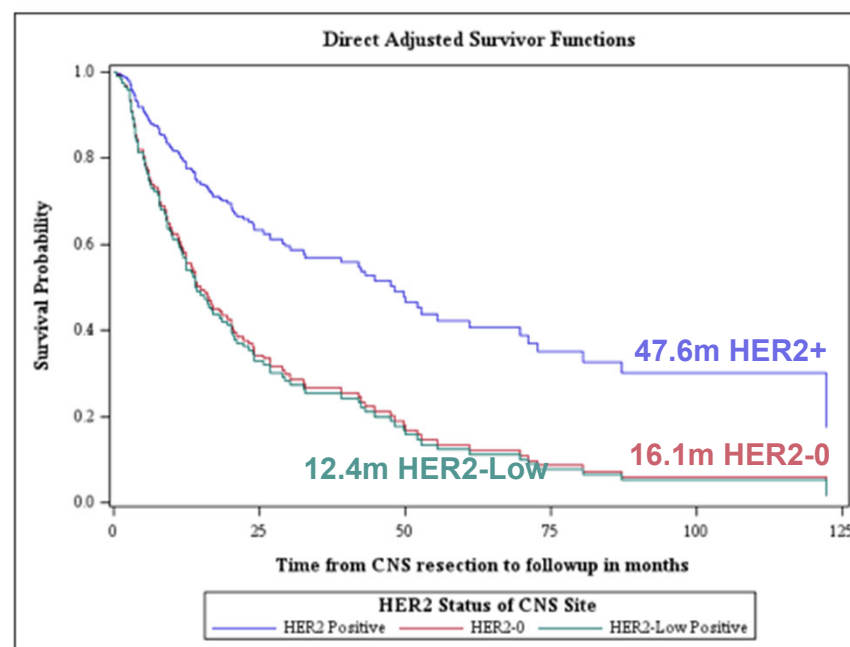


Fig 3. Cox Proportional Hazard Adjusted Survival Curves of HER2+, HER2-0, and HER2-Low



## A Pooled Analysis of Trastuzumab Deruxtecan in Patients With HER2-Positive Metastatic Breast Cancer With Brain Metastases (BMs) from DESTINY-Breast01, -02, and -03

Presentation 3770

**Sara A. Hur**<sup>1</sup>, Shanu Modi, Wei Li, Yeon Hee Park, Wei-Pang Chung, Sung-Bae Kim, Javier Cortes, Toshinari Yamashita, Jose Luiz Pedrini, Seock-Ah Im, Ling-Ming Tseng, Nadia Harbeck, Ian Krop, Giuseppe Curigliano, Elton Mathias, Jillian Cathcart, Antonio Cagnazzo, Shahid Ashfaq, Anton Egorov, Fabrice André

On behalf of the DESTINY-Breast01, -02, and -03 pooled investigators

<sup>1</sup>Fred Hutchinson Cancer Center, University of Washington School of Medicine, Seattle, WA, USA

Madrid, Spain, October 20-24, 2023

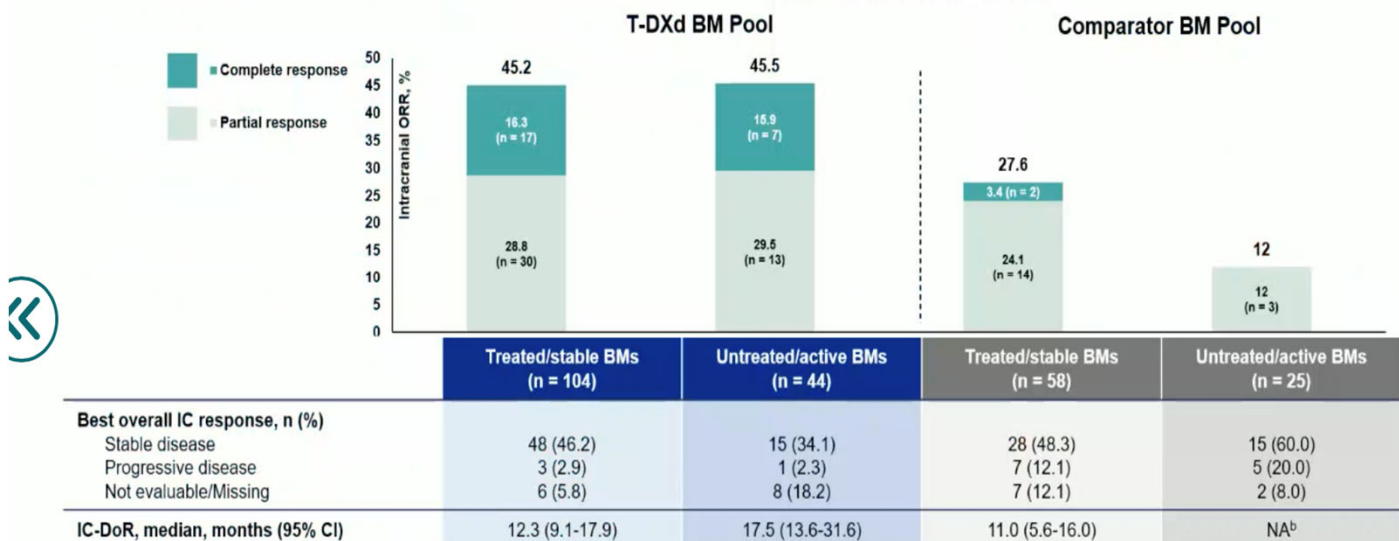




DESTINY-Breast01, -02, and -03

## Exploratory Best IC Response, ORR, and DoR per BICR

### Intracranial ORR<sup>a</sup>



- T-DXd consistently demonstrated superior rates of IC responses over comparator in patients with treated/stable and untreated/active BMs
- A trend in prolonged median IC-DoR was most pronounced in the untreated/active BMs subgroup

BM, brain metastasis; BICR, blinded independent central review; DoR, duration of response; IC, intracranial; NA, not available.

This table considers both target and non-target lesions at baseline. Lesions in previously irradiated areas were not considered measurable target lesions unless there was demonstrated progression in the lesion.

<sup>a</sup>IC-ORR was assessed per RESIST v1.1. <sup>b</sup>IC-DoR NA due to small number of responders (n < 10).



Sara A. Hurvitz, MD

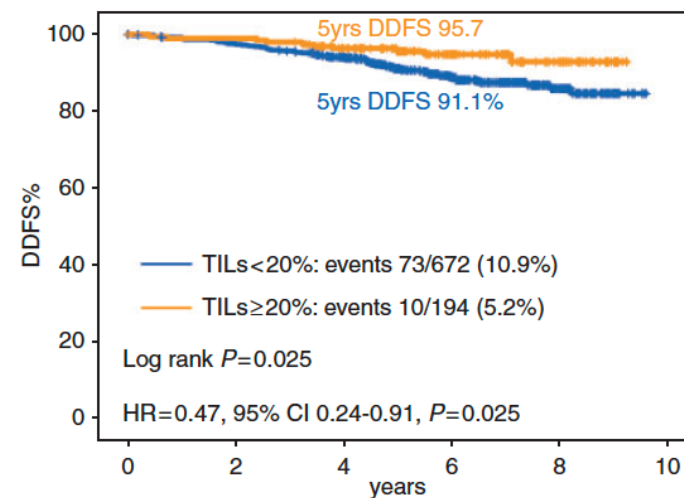
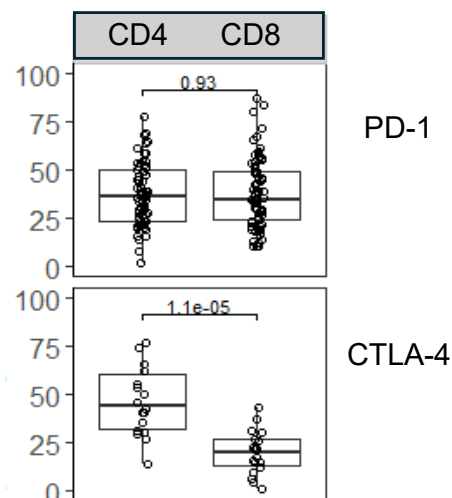
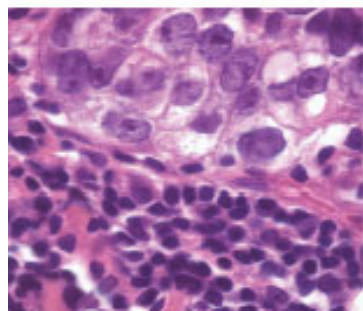
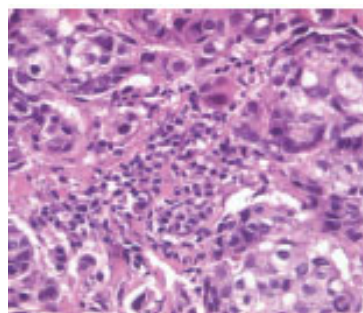
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## Conclusions

- Since 1998, which marked the beginning of the anti-HER2 targeted therapy era, survival rates of patients with metastatic disease have dramatically and progressively improved
- Dual HER2 targeting once again proves successful, and HER2CLIMB-02 paves the way for potential combinations, including with the new ADCs
- Optimal sequencing strategy is the challenge, being attrition rate significant even in the context of clinical trials
- CNS events remain big problem and unmet need



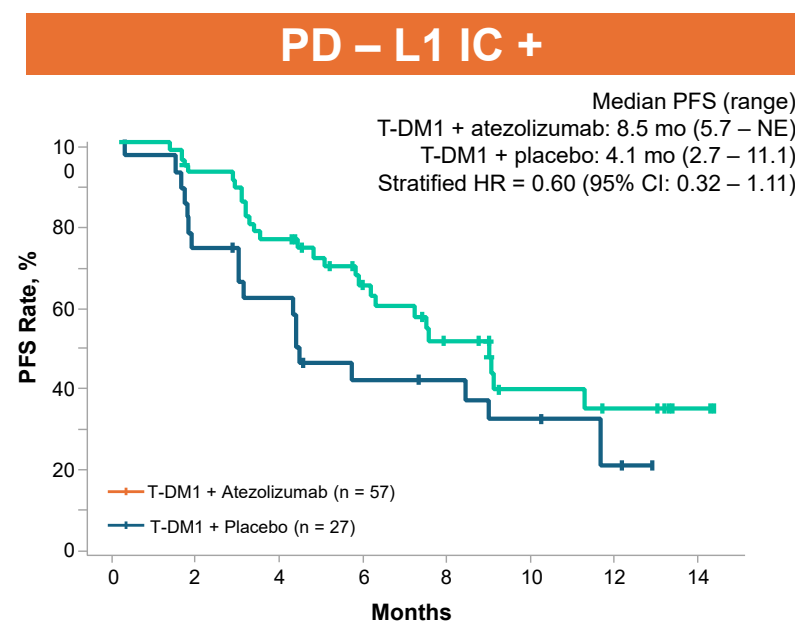
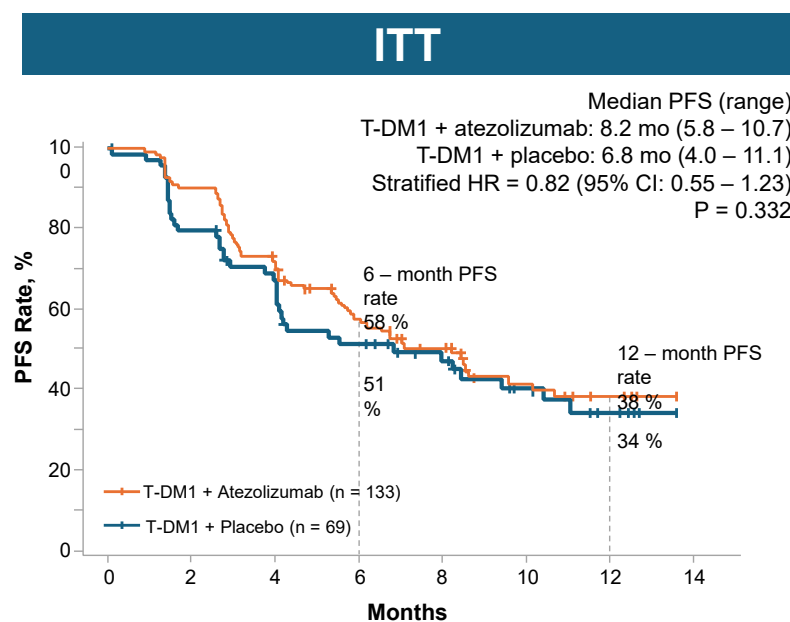
## Immunotherapy: strong rationale to combine HER2- targeted therapy with PD-(L)1 inhibitors



N. at risk						
TILs<20%	672	651	581	329	91	0
TILs≥20%	194	191	168	88	30	0

Savas et al, Nat Med 2019; Dieci MV et al, Short HER 20

## KATE2: PFS in ITT and PD-L1 IC+ populations



HR, Hazard ratio ; IC, tumour-infiltrating immune cells; ITT, intention to treat; NE, not estimable; PFS, progression-free survival  
 CCOD 11th Dec 2017.

Emens LA et al, Lancet Oncology 2020







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