Advances in HER2+ BC

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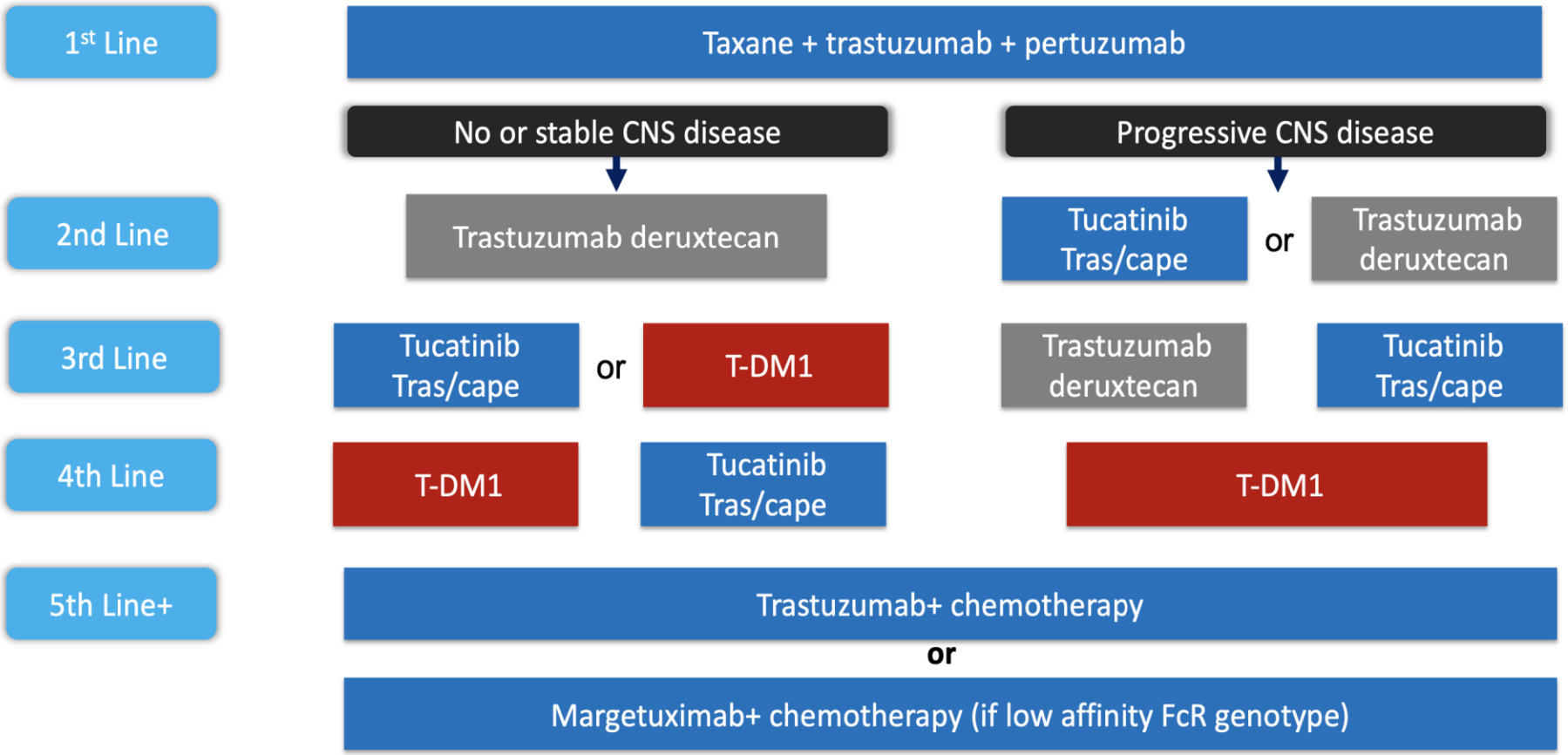
Outline

- MBC
  - Current standards for HER2+ MBC
  - Will TXD-d move up to 1st line?
  - Can the efficacy of tucantinib be enhanced with an ADC?
- Early stage BC
  - Current standards for EBC
    - De-escalating for lower risk disease
    - Duration
  - Managing residual dx after preop
    - Update of Katherine
    - Strategies for escalation or de-escalation based on response clinically, pathologically or by dynamic imaging

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[k]

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

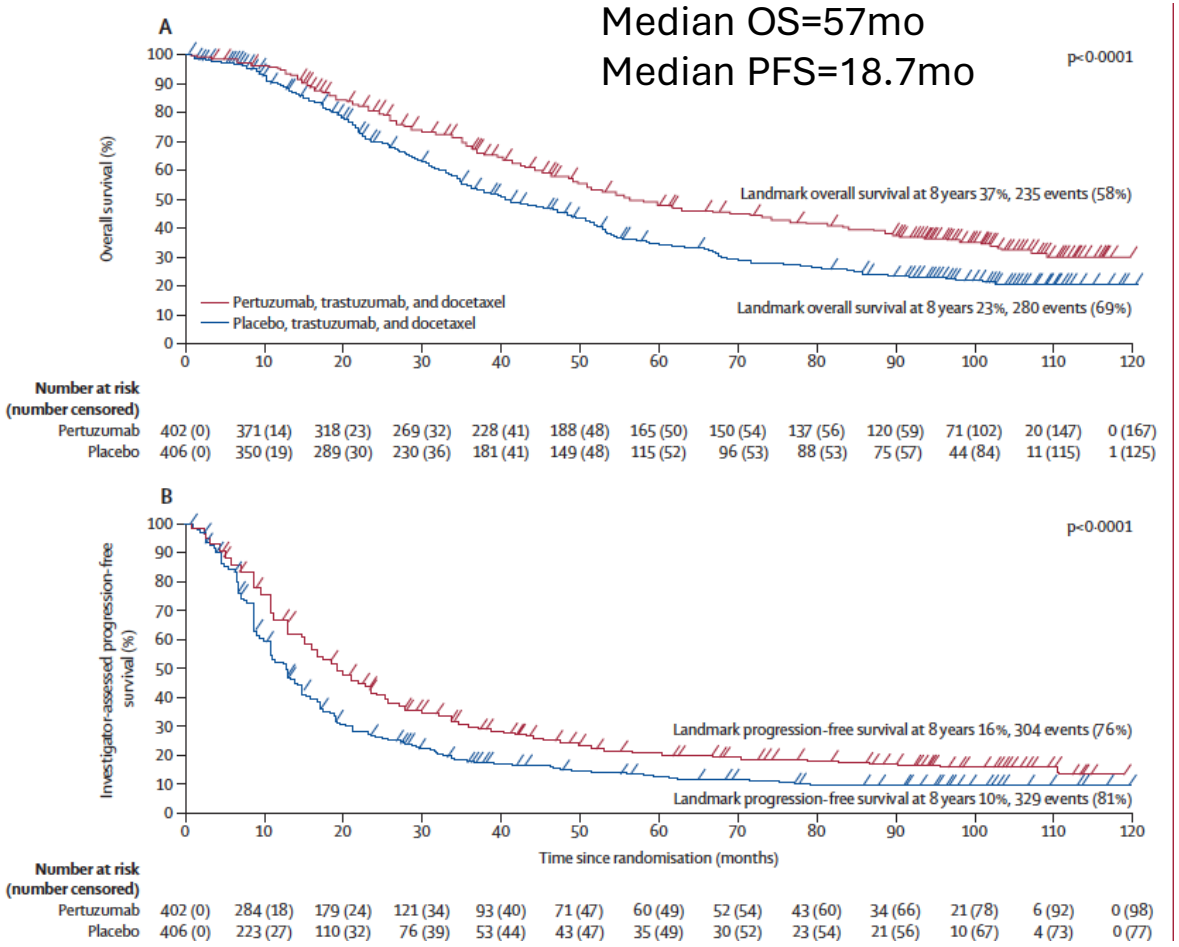
Approach to Therapy for Metastatic HER2+ disease 2024



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

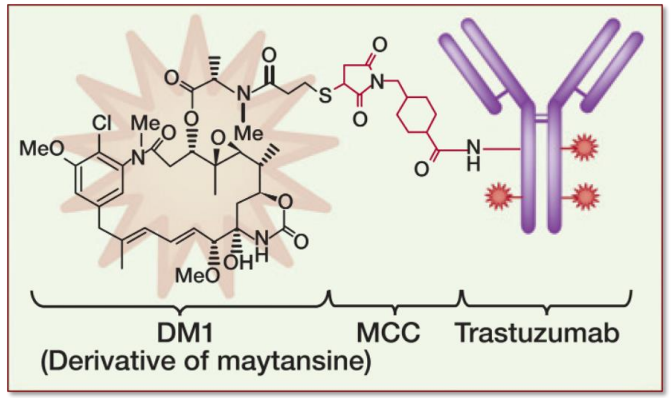
- PR+
- HER2 +3 IHC
- De novo presentation
- have non measurable, non-visceral disease (oligometastatic)
- Tumor *PIK3CA* WT
- Higher HER2 mRNA
- Higher TIL

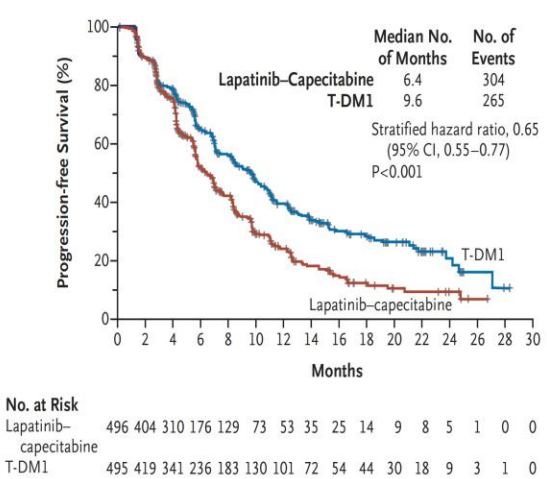
Swain et al, Lancet Oncology 2020 Median FU 99mo

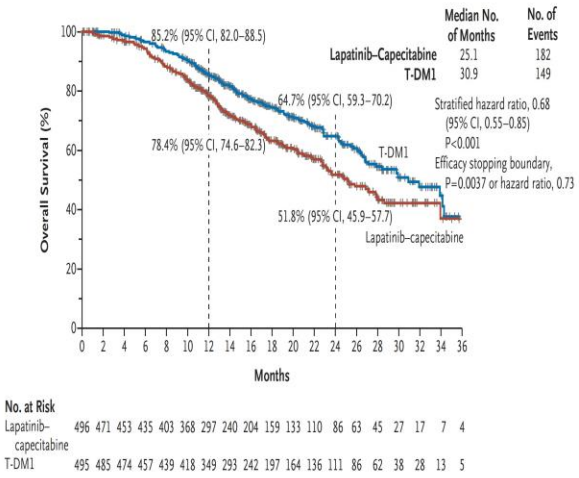
Phase 3 EMILIA: T-DM1 in HER2+ MBC

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)

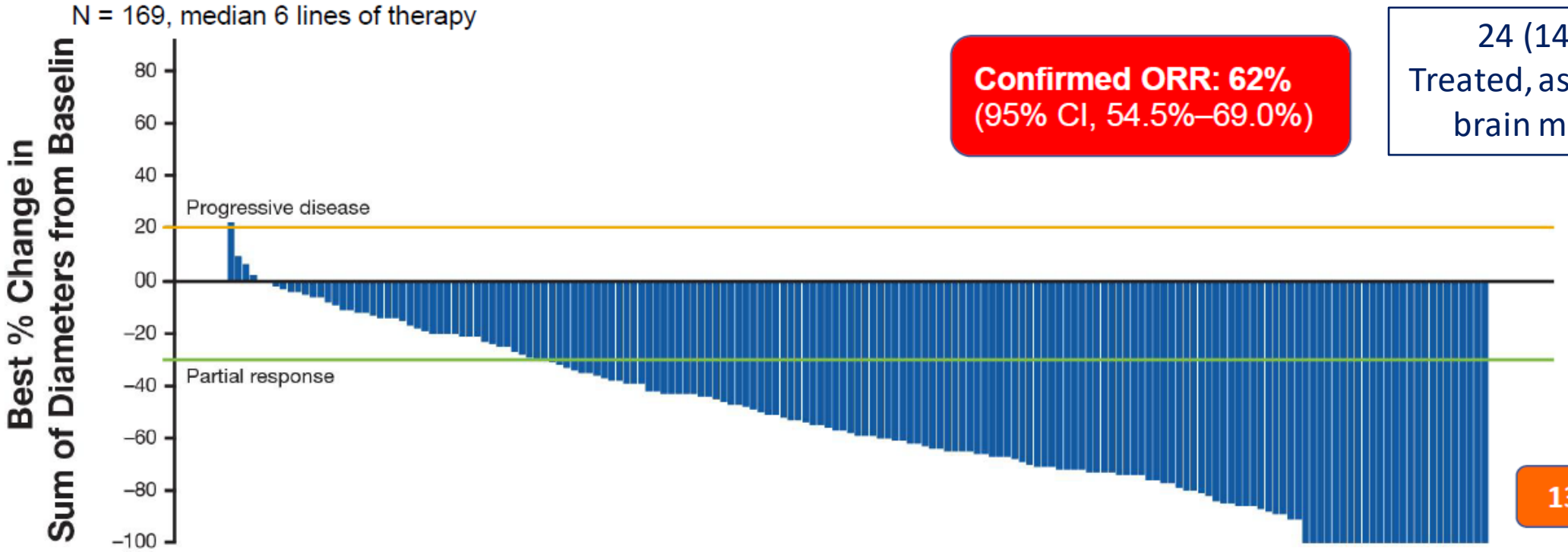






Verma S et al. *N Engl J Med*. 2012;367:1783.

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



Confirmed ORR: 62%
(95% CI, 54.5%–69.0%)

24 (14%) with Treated, asymptomatic brain metastases

13/168 CRs: 7%

Prior therapies:
Trastuzumab 100%
T-DM1 100%,
Pertuzumab 66%

Median PFS was 19.4 months (95% CI, 14.1-25.0 months)
Median OS was 29.1 months (95% CI, 24.6-36.1 months)

NEJM 2020;382:610-21

MADRID 2023 ESMO congress

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

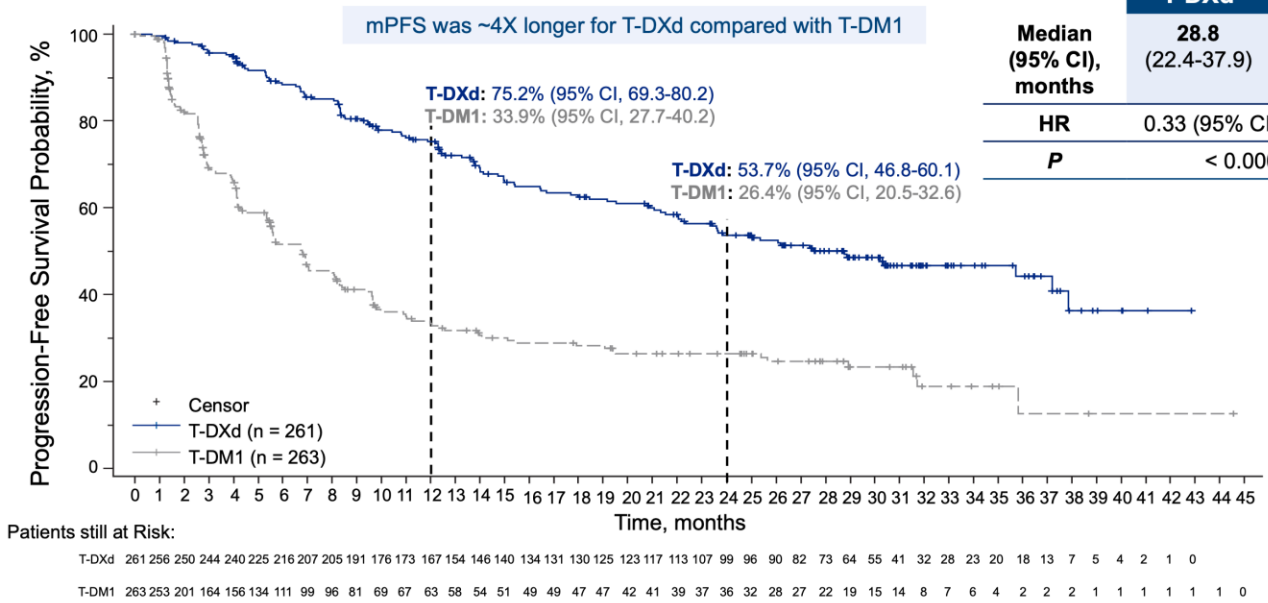
Updated AEs

- ILD: 15.2%, no grade 4 or 5

All grade AE

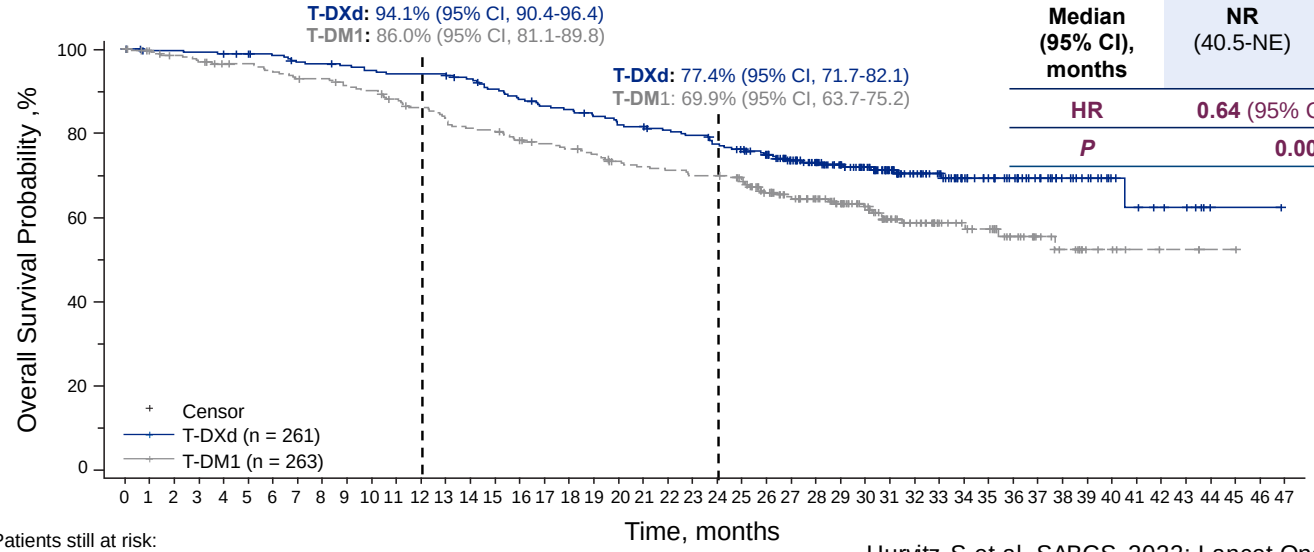
- Nausea: 77%
- Vomiting: 52%
- Alopecia 40%
- Neutropenia ≥grade 3: 16%

Updated Primary Endpoint: PFS by BICR



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

Key Secondary Endpoint: Overall Survival



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

Hurvitz S et al. SABCS 2022; Lancet Oncology 2023

ADCs in sequence?.....benefit?

DESTINY-Breast02: mHER2+ later line T-Dxd vs TPC

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

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)

Majority with 2-3 lines of prior therapy

At data cutoff (June 30, 2022), the median duration of follow-up[d] 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

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)
P < 0.000001

OS

Median (95% CI), months

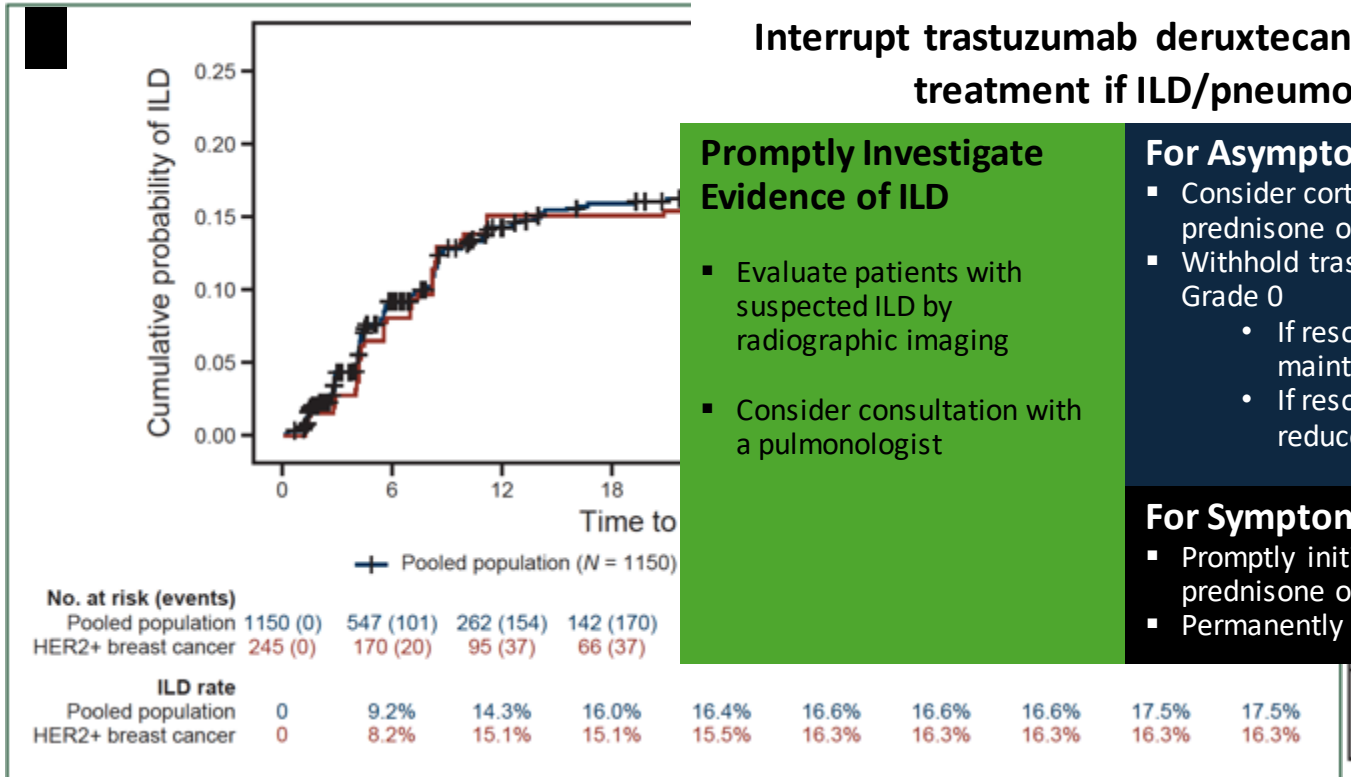
T-DXd	TPC
39.2 (32.7-NE)	26.5 (21.0-NE)

HR (95% CI): 0.6575 (0.5023-0.8605)
P =0.0021[a]

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



Interrupt trastuzumab deruxtecan and initiate corticosteroid treatment if ILD/pneumonitis is suspected

Promptly Investigate Evidence of ILD

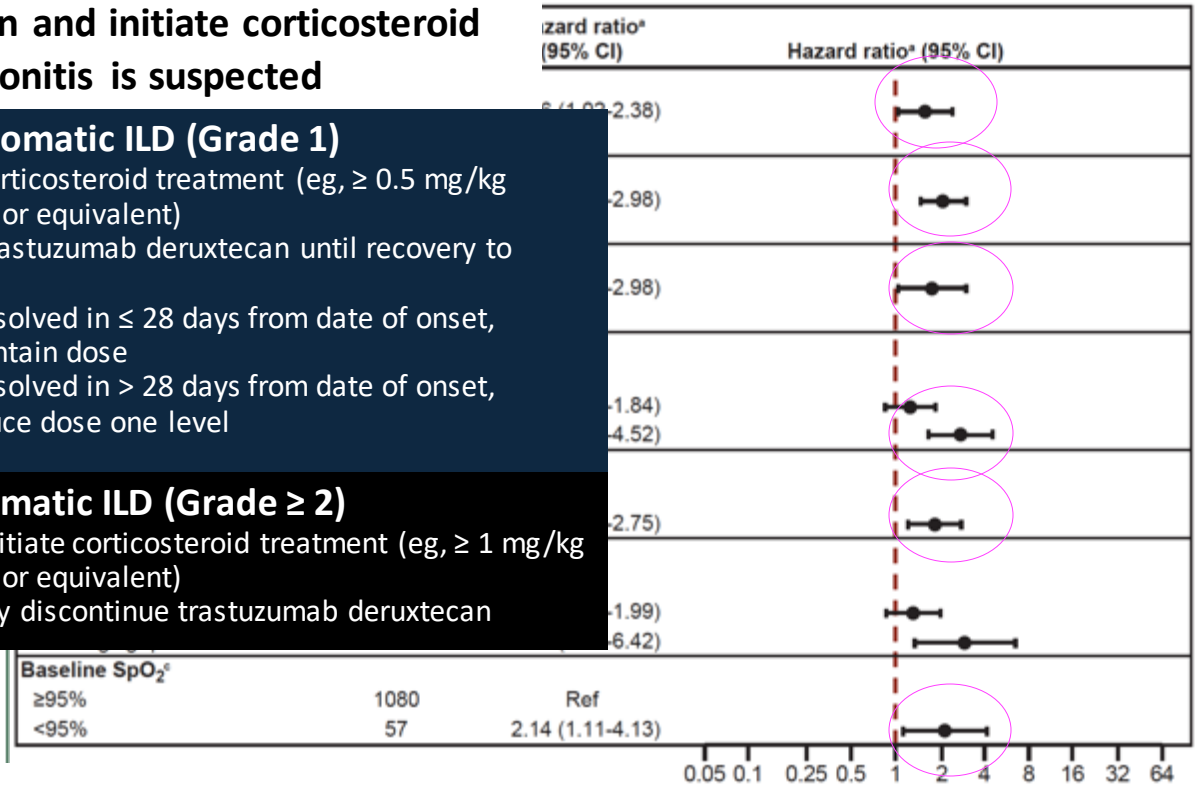
- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

For Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg prednisone or equivalent)
- Withhold trastuzumab deruxtecan until recovery to Grade 0
  - If resolved in ≤ 28 days from date of onset, maintain dose
  - If resolved in > 28 days from date of onset, reduce dose one level

For Symptomatic ILD (Grade ≥ 2)

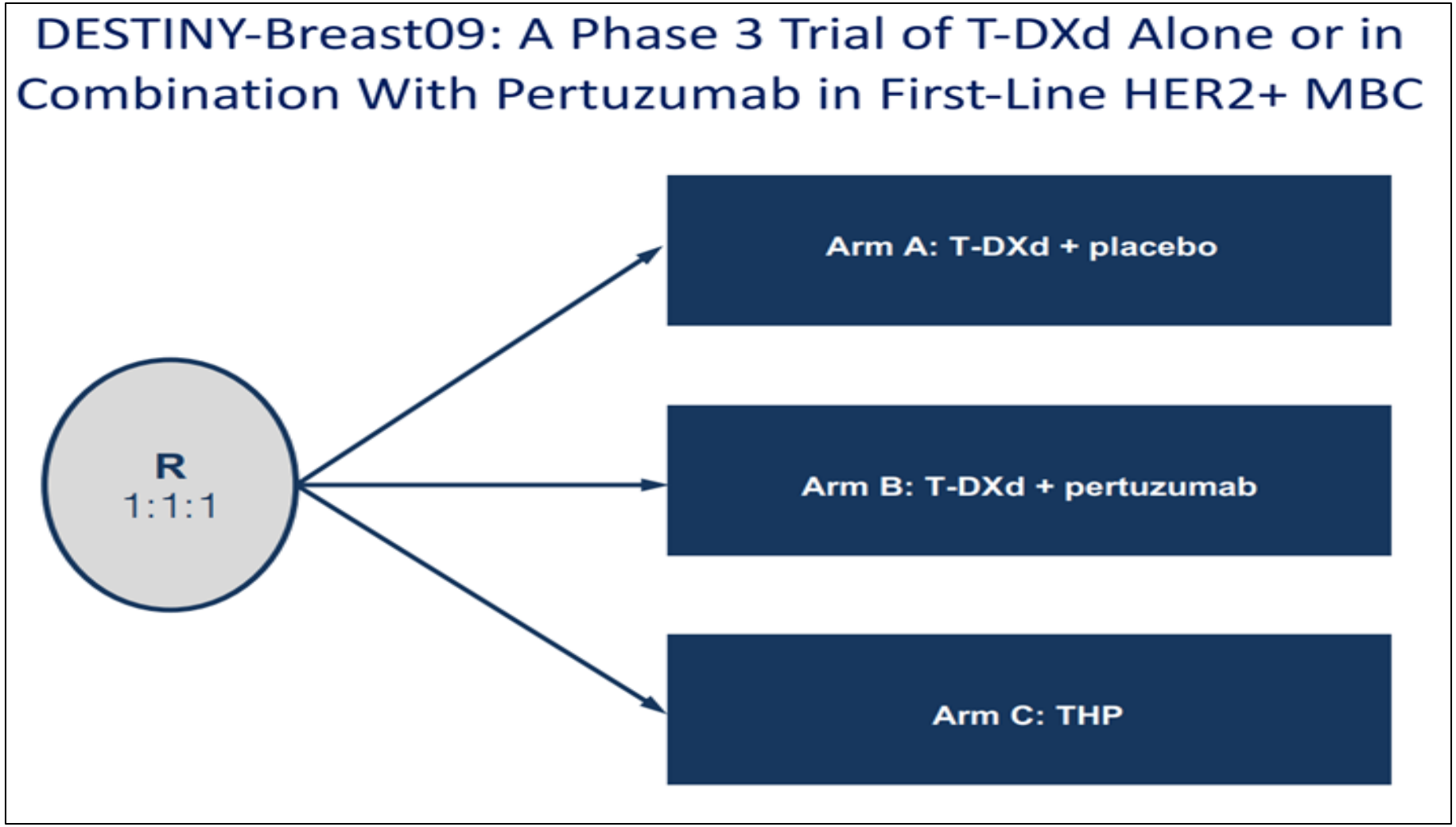
- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan



- 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

T-DXd as first line therapy?

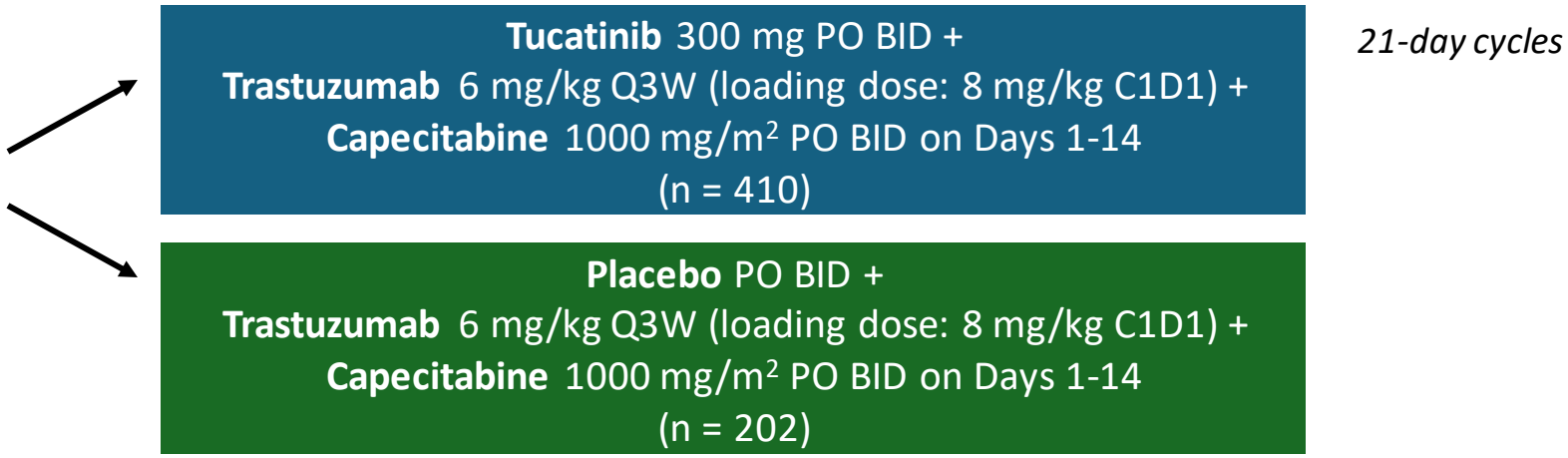


HER2CLIMB: Tucatinib + Trastuzumab + Capecitabine in Previously Treated HER2+ MBC

- 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.



21-day cycles

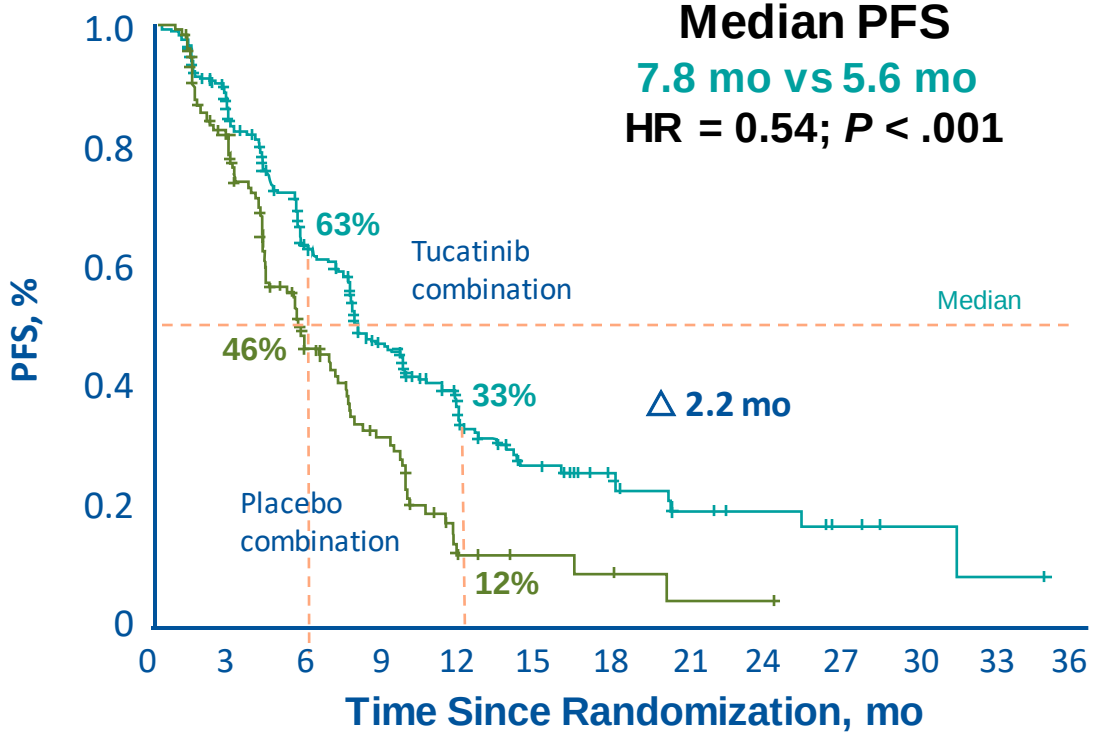
- Primary endpoint: PFS (RECIST v 1.1 by BICR) among first 480 randomized patients
- Secondary endpoints (total population): OS, PFS in patients with brain mets, ORR in patients with measurable disease, safety in patients who received ≥1 dose of study tx

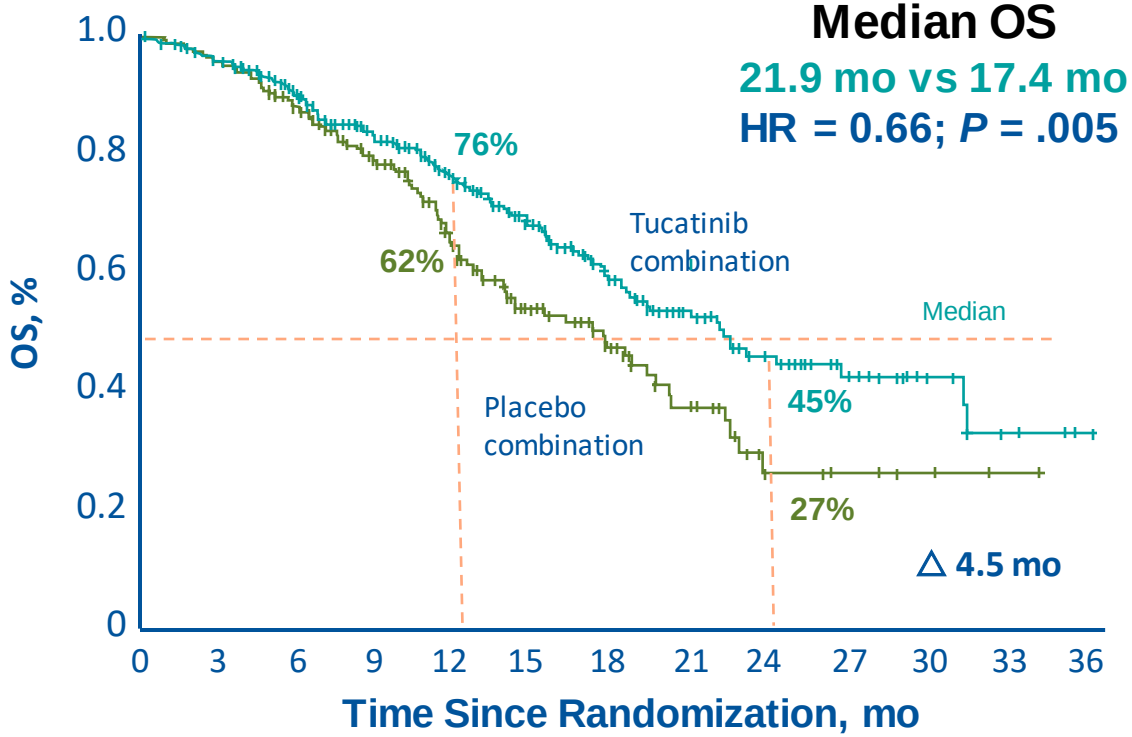
Murthy. NEJM. 2020; 382:597.

HER2CLIMB: Randomized Phase 2 Trial of Tucatinib[1]

Tucatinib + Capecitabine + Trastuzumab vs Capecitabine + Trastuzumab

Tucatinib Improves PFS and OS





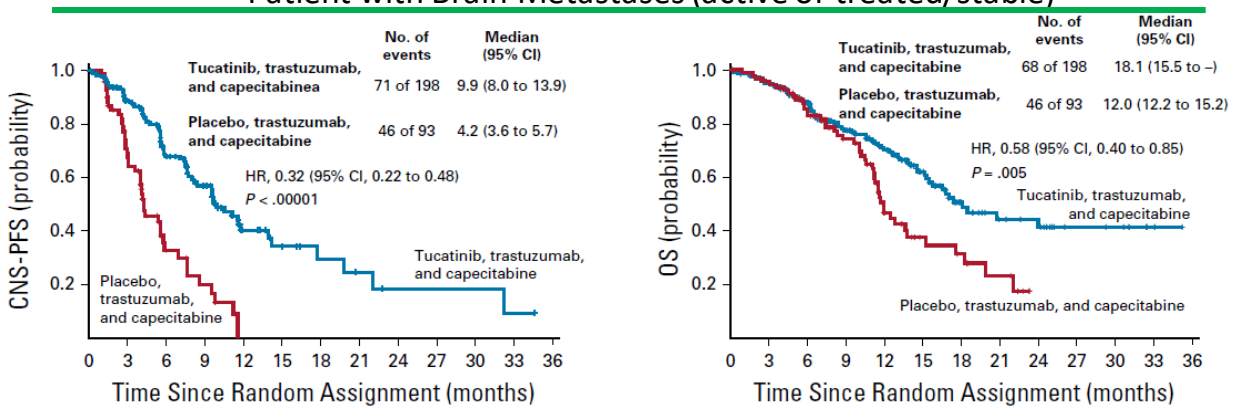
No. at Risk													
Tuc + tras + cape	320	235	152	96	40	29	15	10	8	4	2	1	0
Pbo + tras + cape	160	94	45	27	6	4	2	1	1	0	0	0	0

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

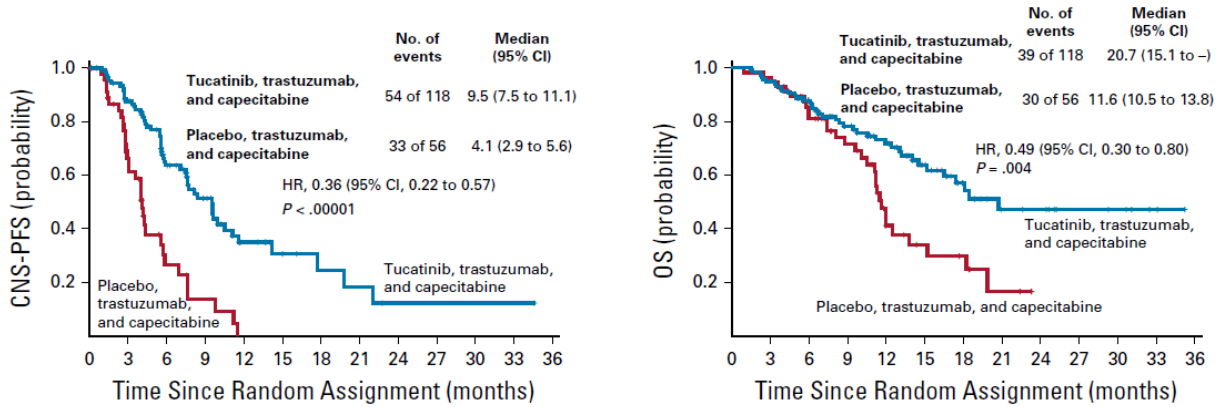
Murthy R, et al. *N Engl J Med* 2020;382:597-609.

Intracranial CNS-Specific Outcomes: HER2CLIMB Study Results

Patient with Brain Metastases (active or treated/stable)



Patient with Brain Metastases (active)

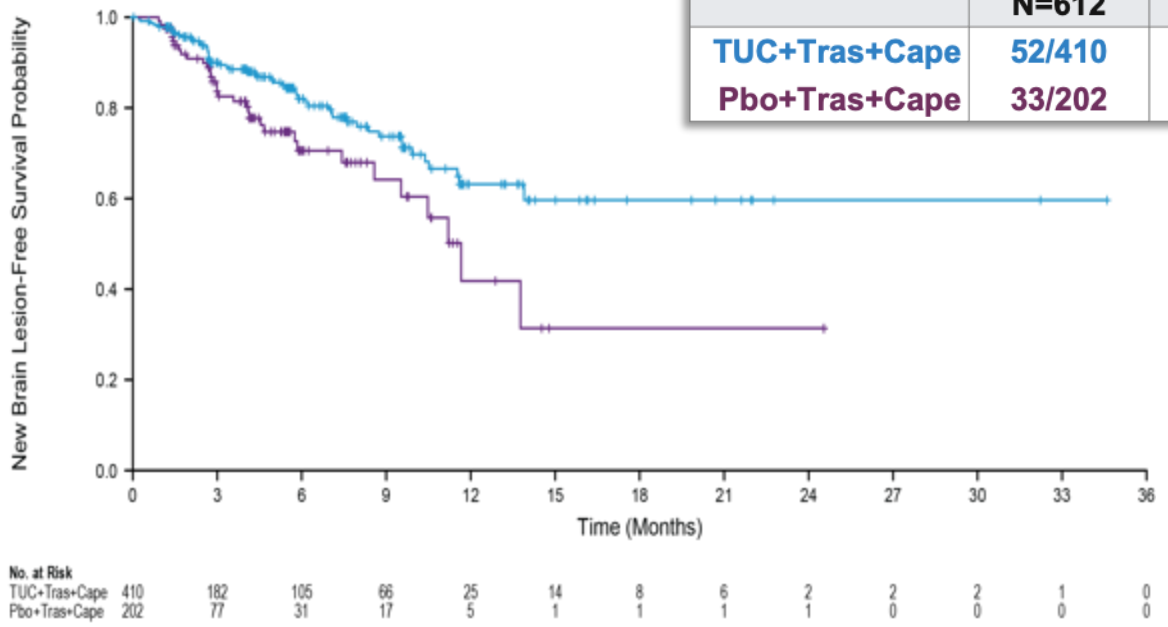


Intra-Cranial CNS Response (RECIST) N=75	Tucatinib N=55 N (%)	Placebo N=20 N (%)
CR	3 (5.5)	1 (5.0)
PR	23 (41.8)	3 (15.0)
SD	24 (43.6)	16 (80.0)
PD	2 (3.6)	0
Not Available	3 (5.5)	0
Confirmed ORR	26 (47.3)	4 (20.0)
95% CI	33.7-61.2%	5.7-43.7%
Stratified p-value	0.03	
DOR (months)	6.8	3.0

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



	Events N=612	HR (95% CI)	P Value
TUC+Tras+Cape	52/410	0.52 (0.33, 0.82)	0.005
Pbo+Tras+Cape	33/202		

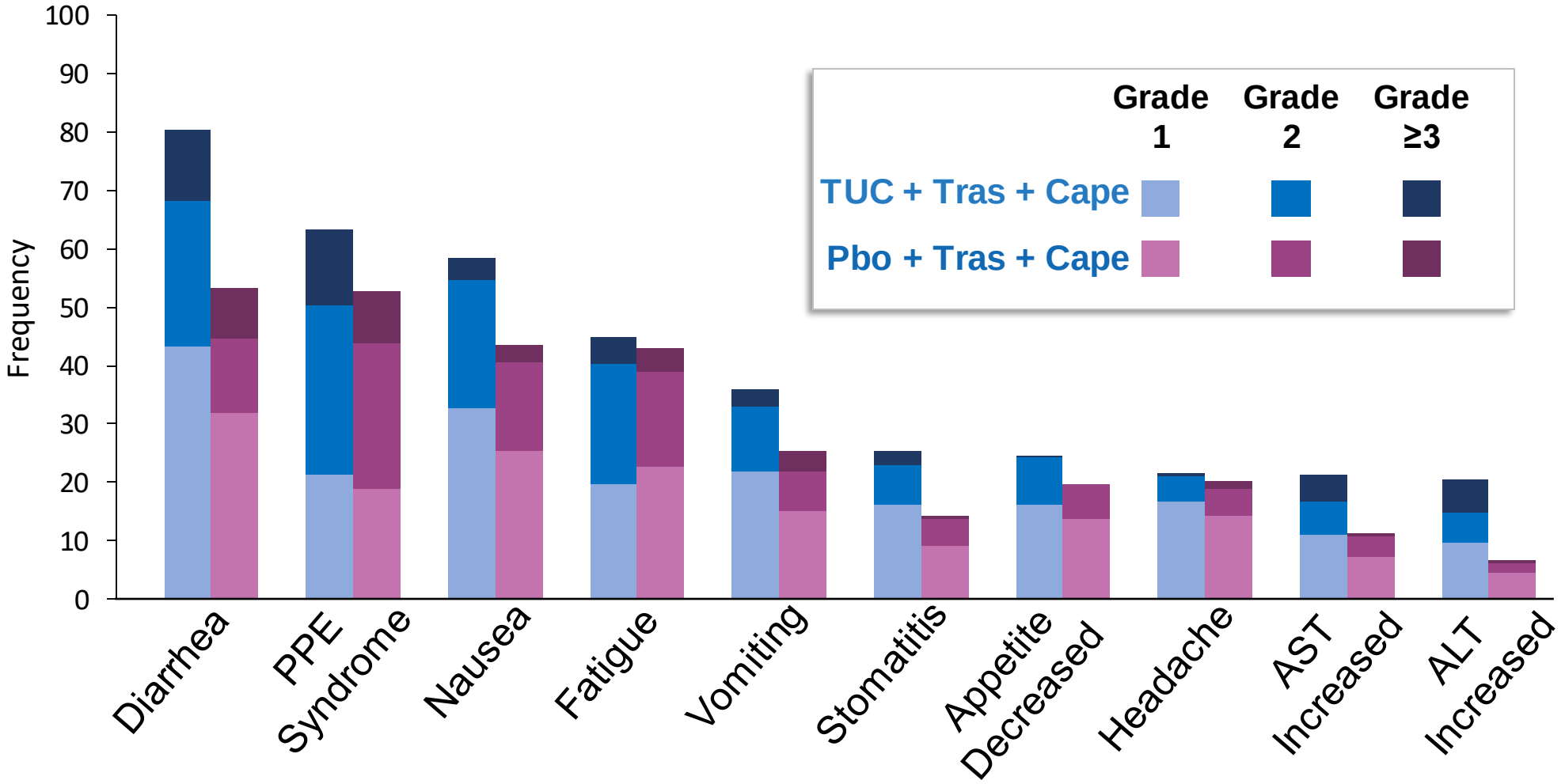
Risk of developing new CNS lesions or death was reduced by 48% in all patients with or without brain metastases in the TUC arm

Median new brain lesion-free survival (95% CI):	
Not reached (13.9, -)	11.7 months (9.5, -)

- 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: 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 137O.

HER2CLIMB-02 Study Design

- 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)

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.[b]

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.
a 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.
b 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.

HER2CLIMB-02: Demographics and Baseline Characteristics

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

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

Hurvitz S, et al. SABCS 2023

a Includes 2 patients with missing brain metastases data.
b 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.

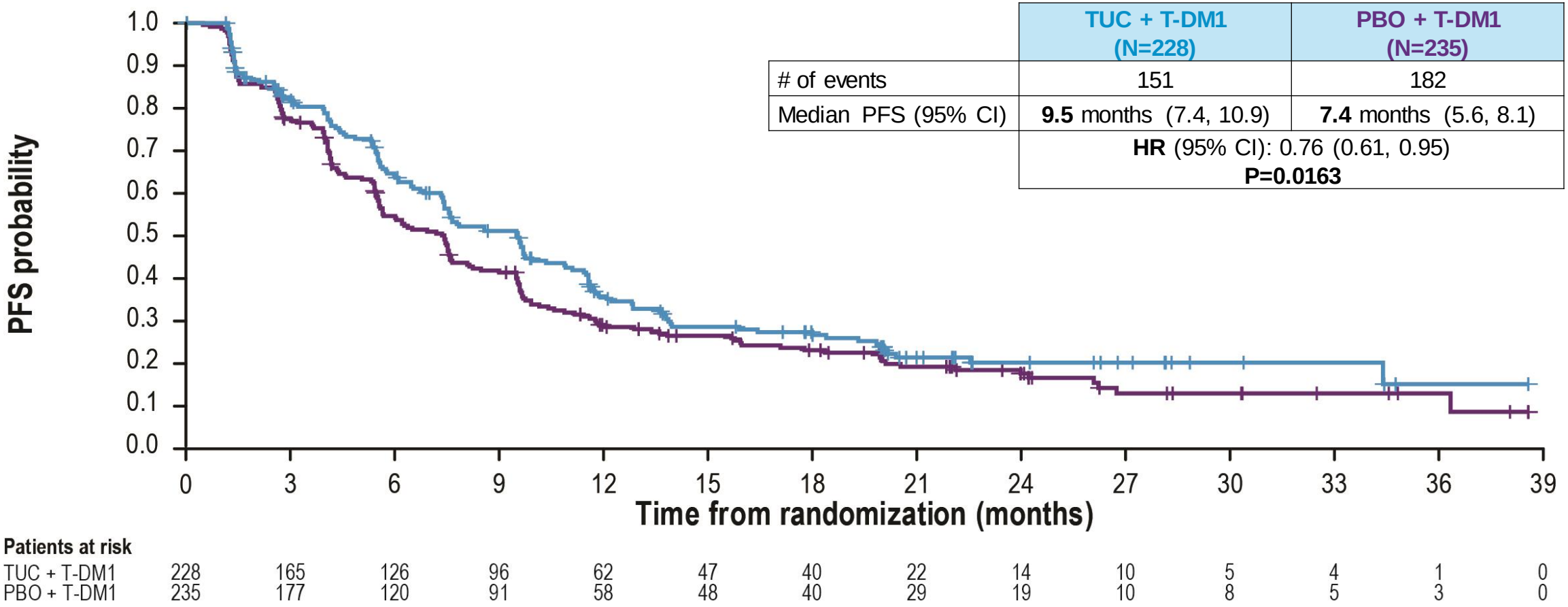
HER2CLIMB-02: Prior Systemic Therapies

	TUC + T-DM1 (N=228)	PBO + T-DM1 (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: Progression-Free Survival

	TUC + T-DM1 (N=228)	PBO + T-DM1 (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**	

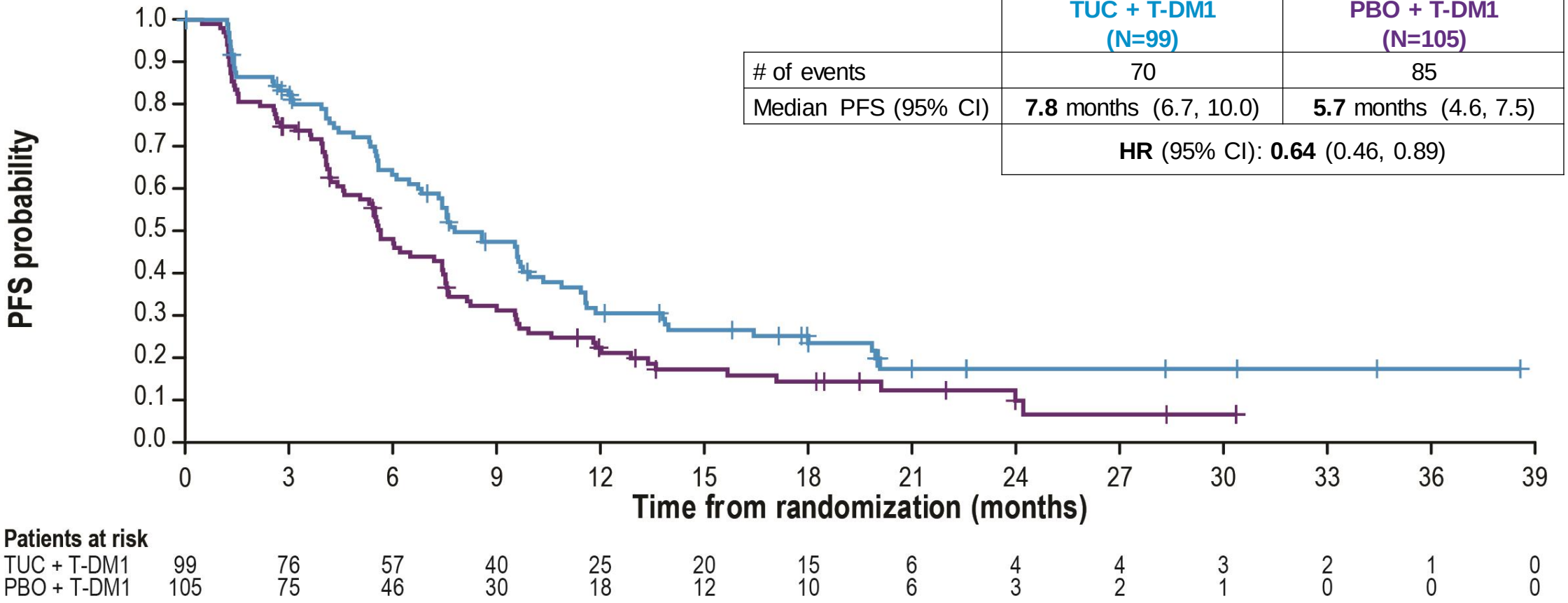


HR, hazard ratio; PBO, placebo; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TUC, tucatinib.
Date of data cutoff: Jun 29, 2023.

Hurvitz S, et al. SABCS 2023

HER2CLIMB-02: PFS in Patients with Brain Metastases[a]

	TUC + T-DM1 (N=99)	PBO + T-DM1 (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): **0.64** (0.46, 0.89)	

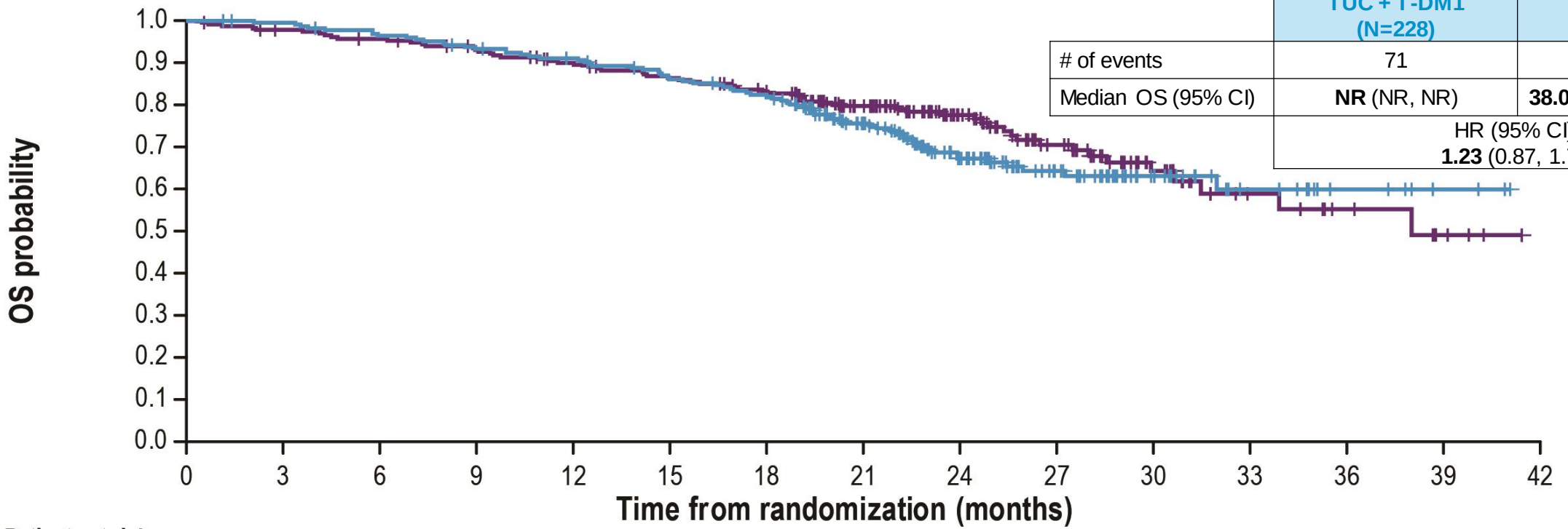


a The outcome was not formally tested.
HR, hazard ratio; PBO, placebo; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TUC, tucatinib.
Date of data cutoff: Jun 29, 2023.

Hurvitz S, et al. SABCS 2023

HER2CLIMB-02: Overall Survival

	TUC + T-DM1 (N=228)	PBO + T-DM1 (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)	



Patients at risk

TUC + T-DM1	228	225	217	209	202	189	180	132	89	55	30	16	7	3	0
PBO + T-DM1	235	227	221	212	201	191	180	135	90	58	32	16	10	4	0

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.

a 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

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[a]

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 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)
Treatment discontinuation		
TUC/PBO	16 (6.9)	5 (2.1)
T-DM1	18 (7.8)	5 (2.1)

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)
Treatment discontinuation		
TUC/PBO	1 (0.4)	0
T-DM1	0	0

a 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

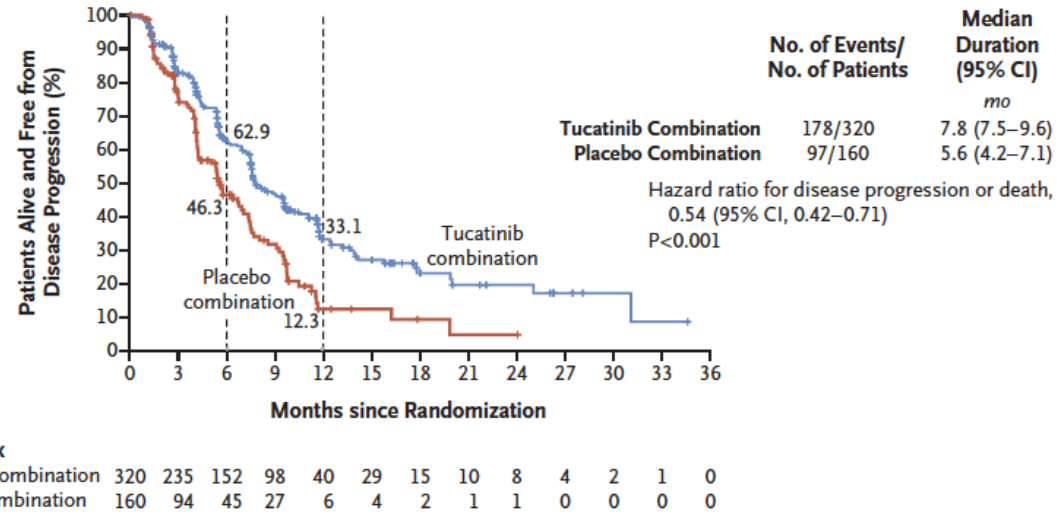
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 13, 2020 VOL. 382 NO. 7

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

Results HER2climb-02 How to incorporate?

A Kaplan–Meier Estimates of Progression-free Survival



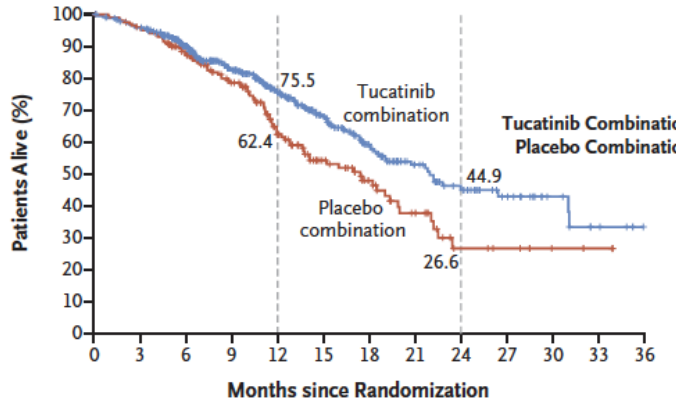
	No. of Events/ No. of Patients	Median Duration (95% CI) mo
Tucatinib Combination	178/320	7.8 (7.5–9.6)
Placebo Combination	97/160	5.6 (4.2–7.1)

Hazard ratio for disease progression or death, 0.54 (95% CI, 0.42–0.71)
P<0.001

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

A Kaplan–Meier Estimates of Overall Survival



	No. of Deaths/ No. of Patients	Median Duration (95% CI) mo
Tucatinib Combination	130/410	21.9 (18.3–31.0)
Placebo Combination	85/202	17.4 (13.6–19.9)

Hazard ratio for death, 0.66 (95% CI, 0.50–0.88)
P=0.005

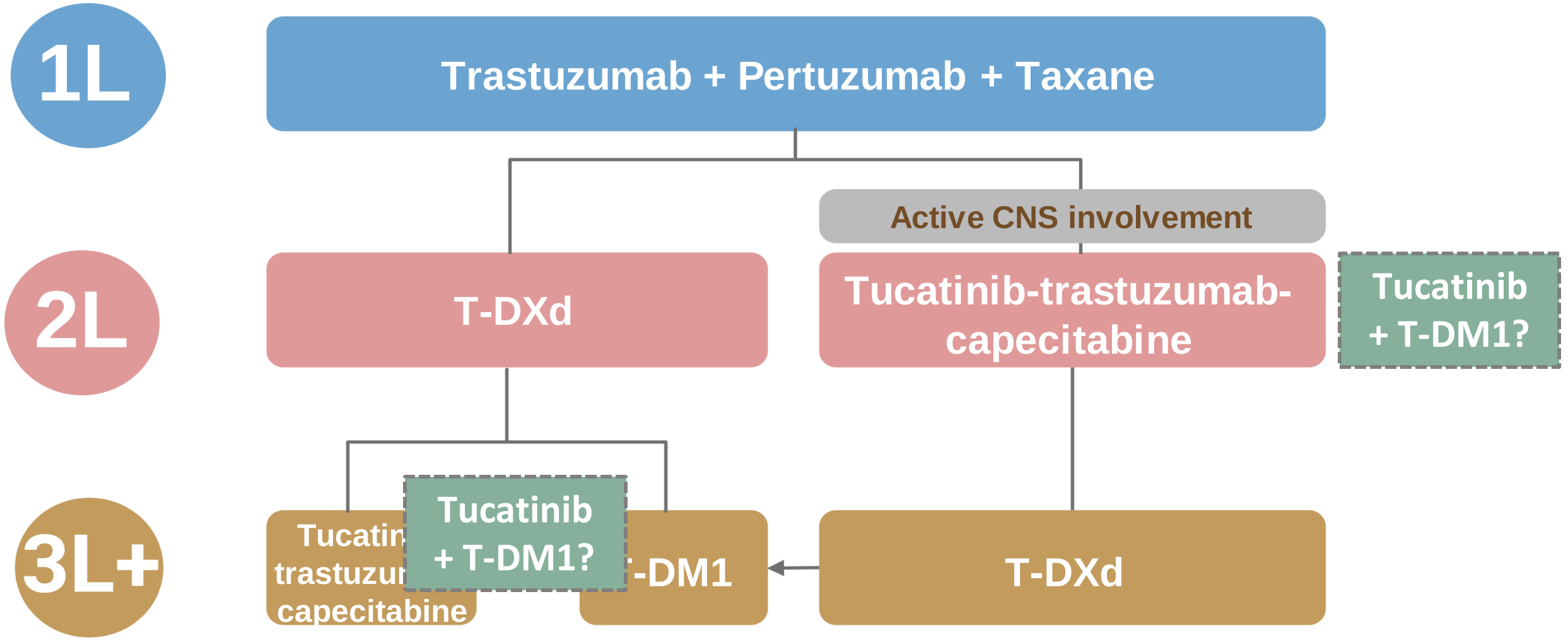
No. at Risk

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

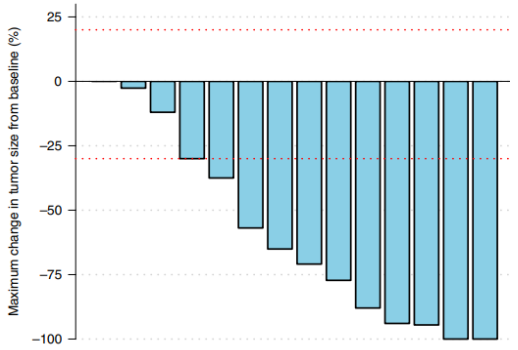
Active untreated brain metastases was eligible, including those >2cm

Current algorithm: where will HER2CLIMB-02 fit in?



Trastuzumab Deruxtecan in pts with active brain mets

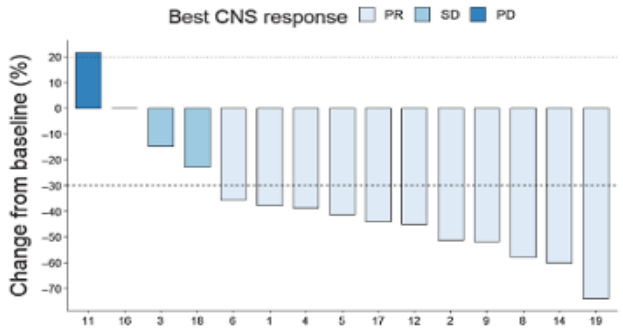
TUXEDO-1 study (n=15)



Intracranial RR = 73.3%

DFCI/MDACC/Duke (n=15*)

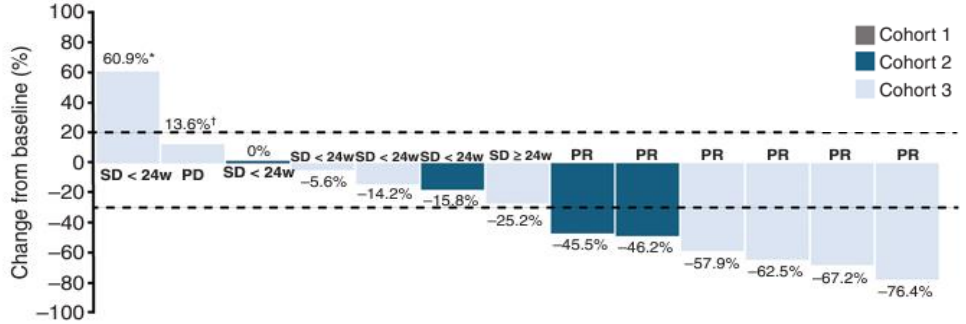
*15/17 with evaluable intracranial RR



Intracranial RR = 73%

DEBBRAH (n=13*)

*active BM cohorts (2 and 3)



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

MADRID 2023 ESMO congress

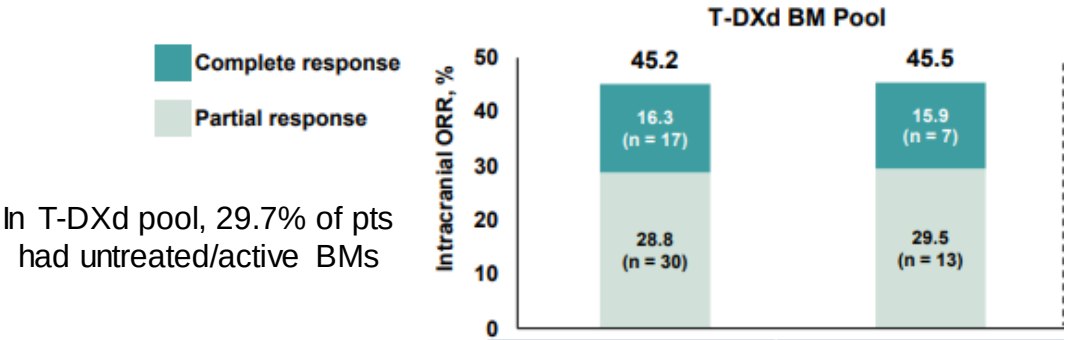
A Pooled Analysis of Trastuzumab Deruxtecan in Patients With HER2-Positive Metastatic Breast Cancer With Brain Metastases (BMs) from DESTINY-Breast01, -02, and -03

Presentation 3770

Sara A. Hurvitz[1], 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 Ashfaque, Anton Egorov, Fabrice André

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

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

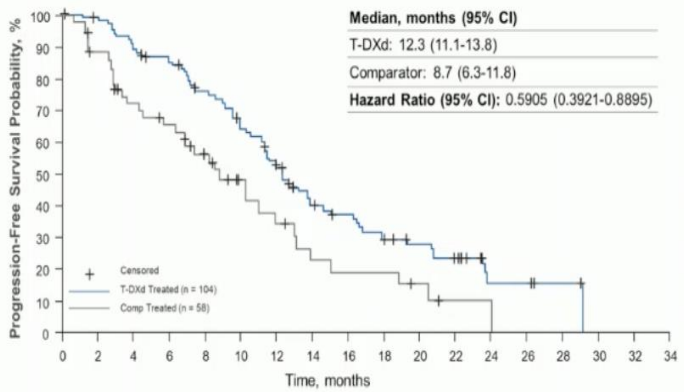


	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)
Best overall IC response, n (%)		
Stable disease	48 (46.2)	15 (34.1)
Progressive disease	3 (2.9)	1 (2.3)
Not evaluable/Missing	6 (5.8)	8 (18.2)
IC-DoR, median, months (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)

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

Exploratory CNS-PFS per BICR

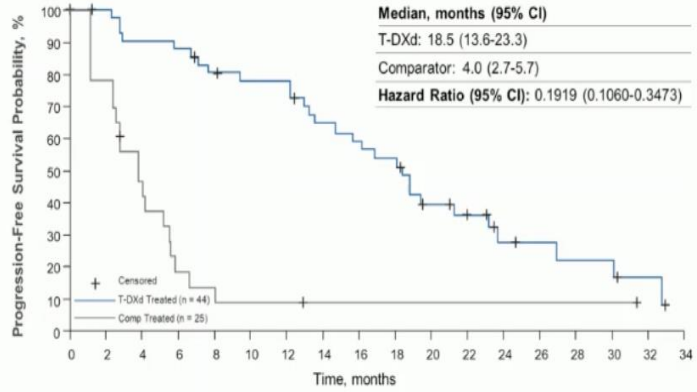
Treated/Stable BMs



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



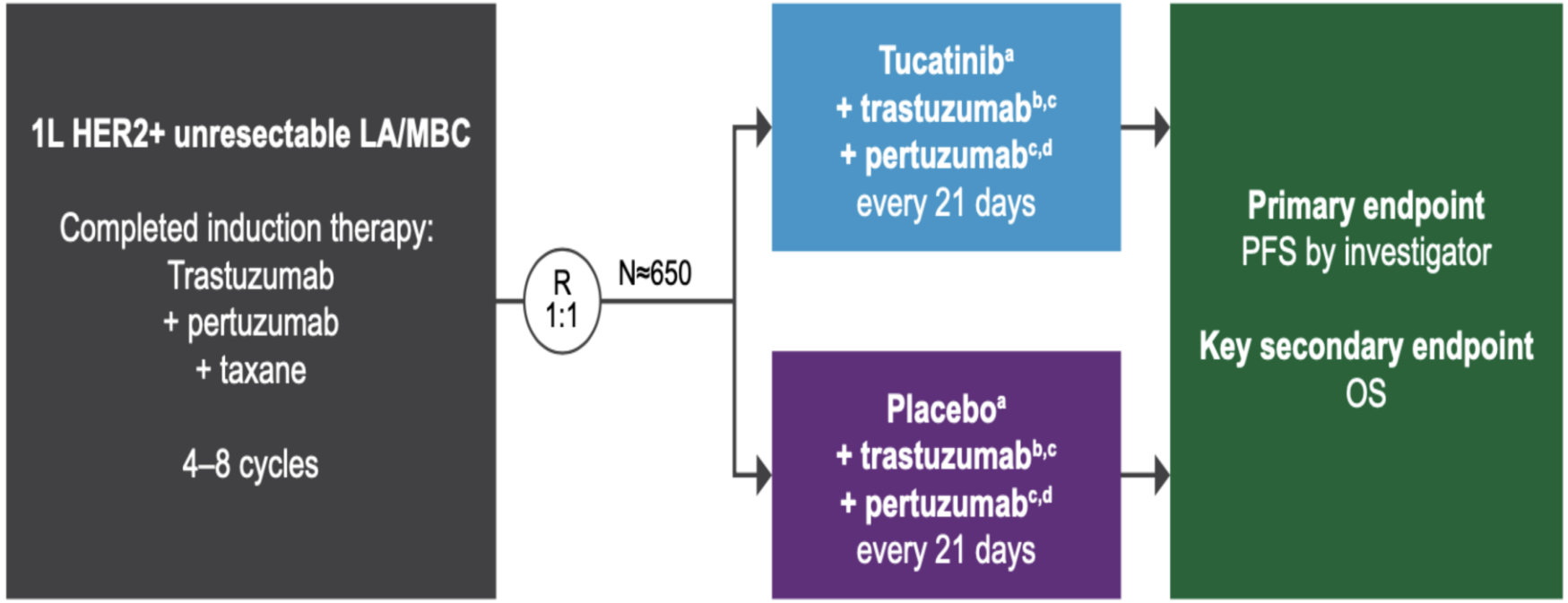
Patients still at risk

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.

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

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[1], Jose Pablo Leone[1], Thibaut Sanglier[2], Peter Lambert[3], Filippo Montemurro[2], Raf Poppe[2], Eleonora Restuccia[2], Sara M. Tolaney[4], Nancy U. Lin[4]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [3]Genentech, Inc., South San Francisco, CA; [4]Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

Sarah L. Sammons, MD

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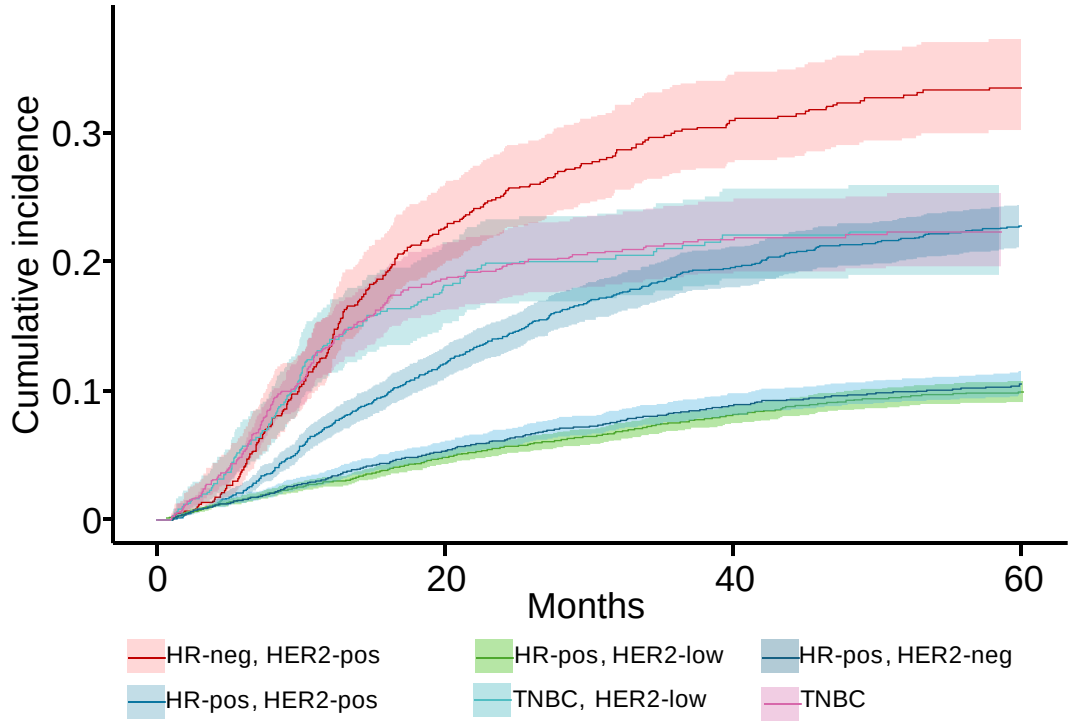
Research funding from: AstraZeneca, AbbVie, Bristol Myers Squibb, Eli Lilly, Seagen, and Sermonix.
Consulting fees from: Foundation Medicine, Inc., AstraZeneca, Daiichi Sankyo, Eli Lilly, Incyclix, Merck, Pfizer, Seagen, Sermonix, and Novartis. Please refer to the abstract for all author conflicts of interest. All authors have received research support in the form of third-party writing assistance for this Spotlight Session presentation from F. Hoffmann-La Roche Ltd. This analysis was funded by F. Hoffmann-La Roche Ltd.

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.

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

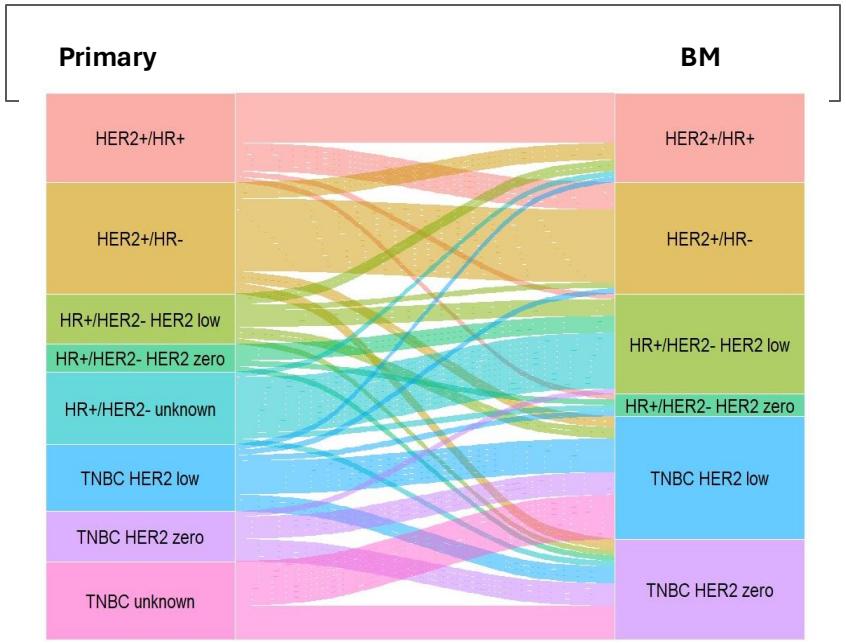
Herbert Wertheim College of Medicine, Miami FL

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%)



Guadalupe A. Garcia, SABCS2023

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

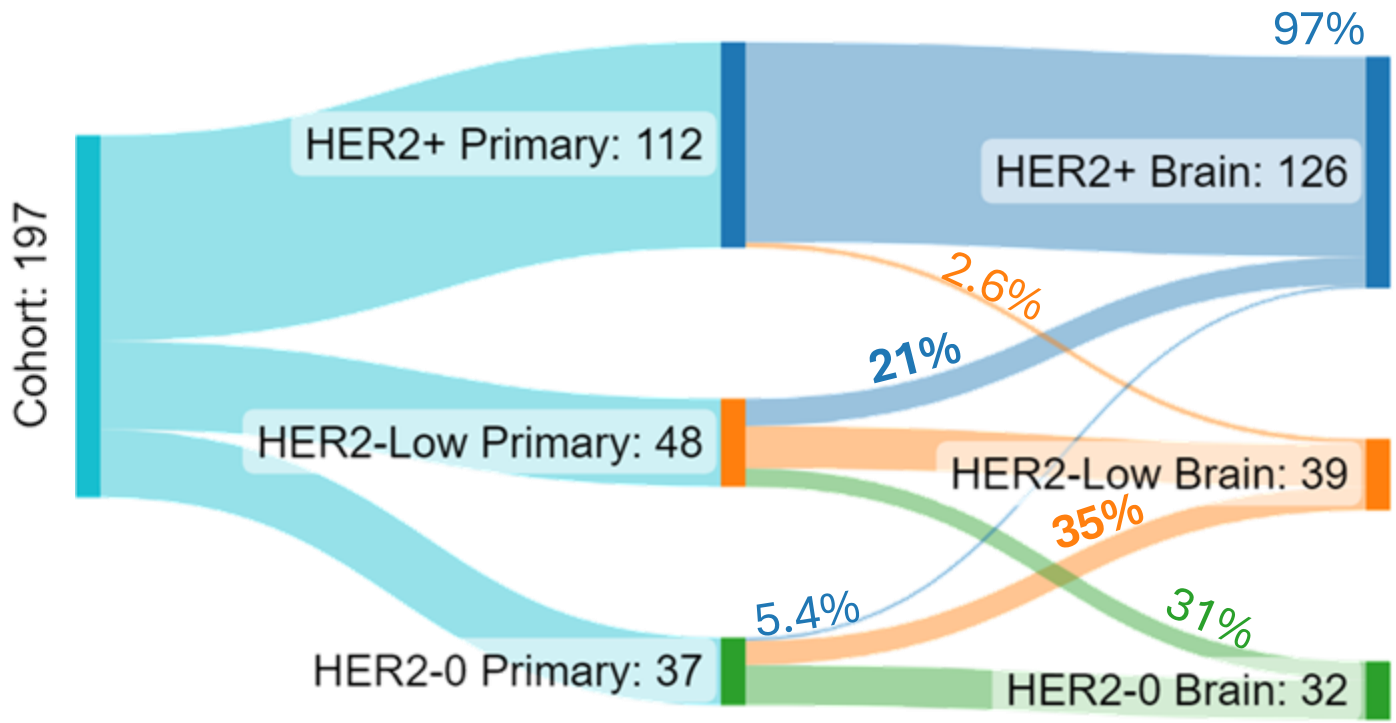


Fig. 2 Subtype Switching From Primary to Brain Metastases (N=197 pairs)

Alyssa M. Pereslete , SABCS2023

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

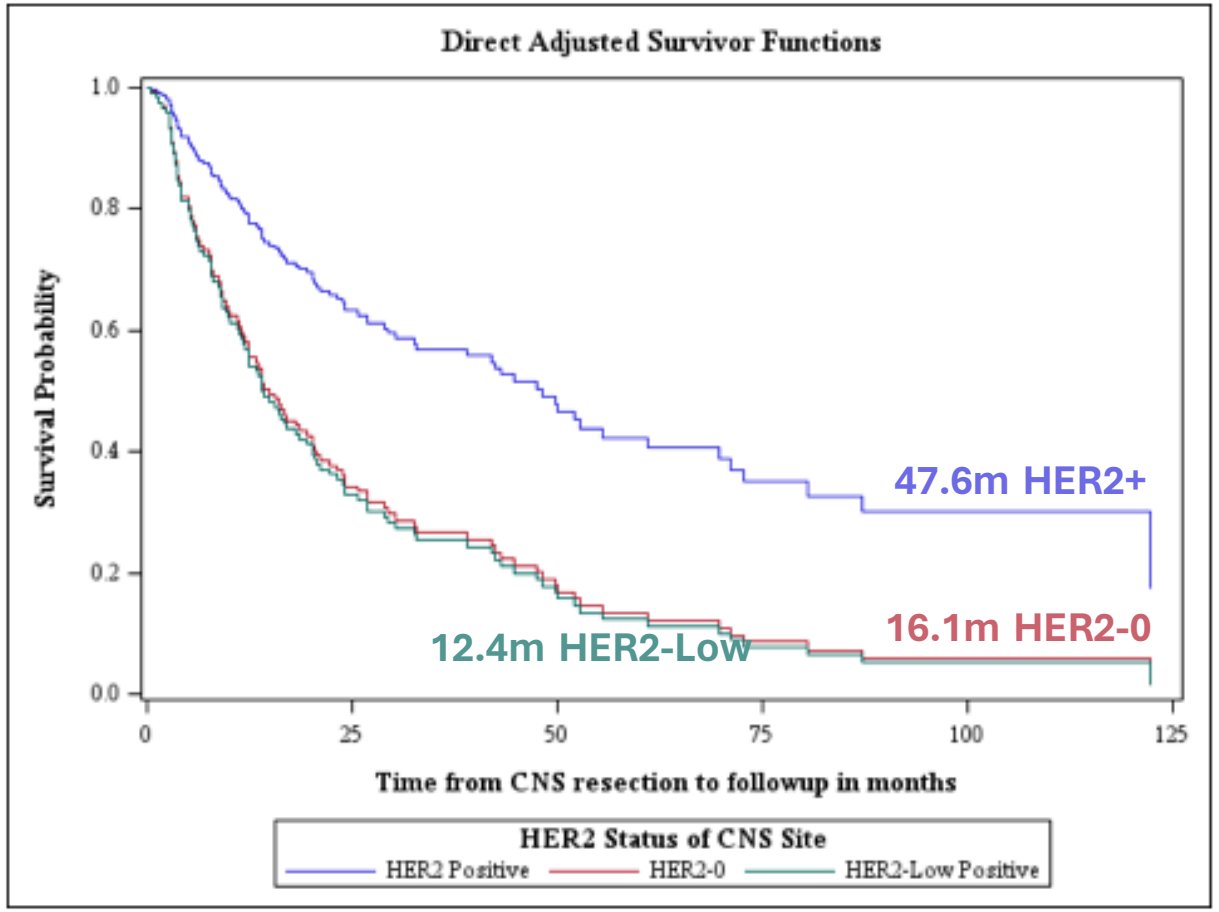


Fig 3. Cox Proportional Hazard Adjusted Survival Curves of HER2+, HER2-0, and HER2-Low

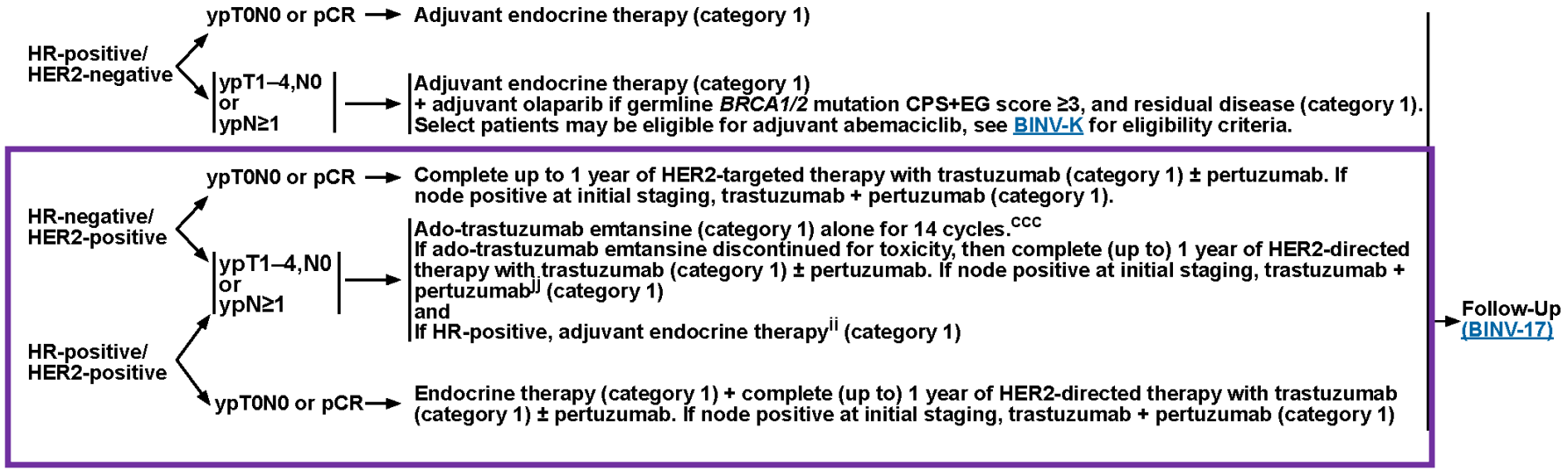
Conclusions

- 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

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

<table>
<tr><th colspan="2">HER2-Positive</th></tr>
<tr><td colspan="2"><u>Preferred Regimens</u>:
• Paclitaxel + trastuzumab[f]
• TCH (docetaxel/carboplatin/trastuzumab)
• TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab)
• If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[j] (category 1) ± pertuzumab.
• If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[g,h] If node positive at initial staging, trastuzumab + pertuzumab (category 1)[i]</td></tr>
<tr><td>Useful in Certain Circumstances:
• Docetaxel + cyclophosphamide + trastuzumab
• AC followed by T[b] + trastuzumab[h] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
• AC followed by T[b] + trastuzumab + pertuzumab[h] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules)
• Neratinib[g] (adjuvant setting only)
• Paclitaxel + trastuzumab + pertuzumab[h]
• Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)</td><td>Other Recommended Regimens:
• AC followed by docetaxel[b] + trastuzumab[h] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab)
• AC followed by docetaxel[b] + trastuzumab + pertuzumab[h] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)
• Paclitaxel/carboplatin + trastuzumab + pertuzumab</td></tr>
</table>

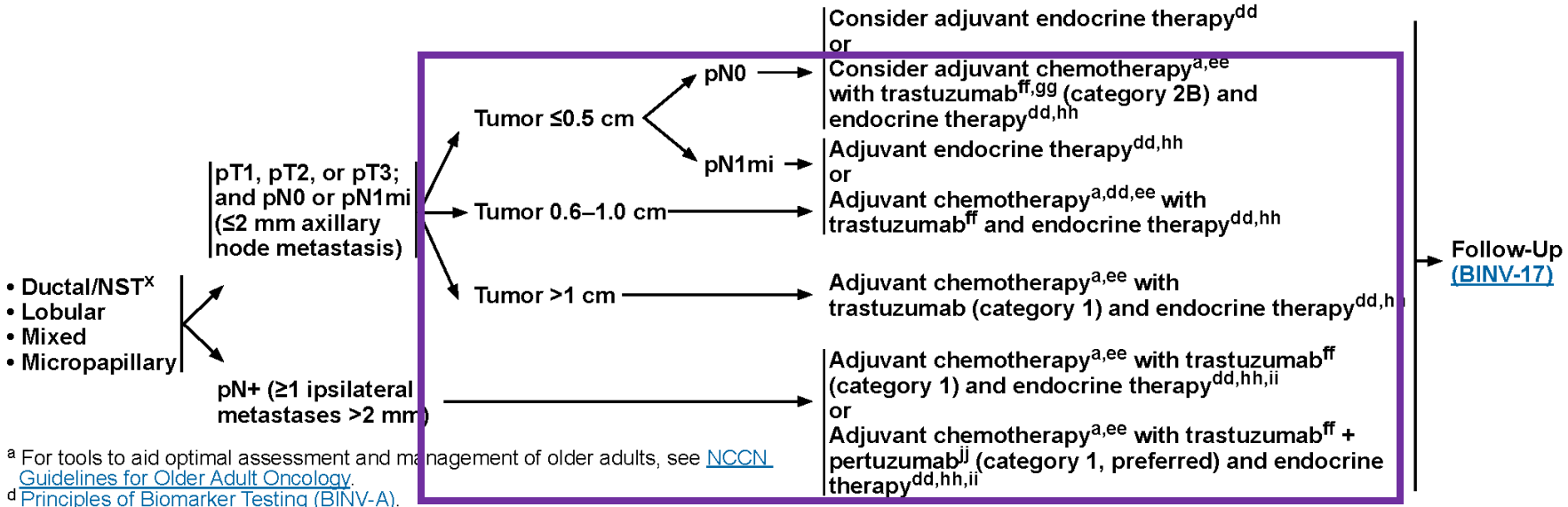
ADJUVANT SYSTEMIC THERAPY AFTER PREOPERATIVE SYSTEMIC THERAPY[hh]



[dd] Principles of Adjuvant Endocrine Therapy (BINV-K).
[ee] Preoperative/Adjuvant Therapy Regimens (BINV-L).
[hh] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[ii] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab or ado-trastuzumab emtansine is unknown.
[jj] Updated results from the adjuvant APHINITY trial in HER2-positive early breast cancer, with a median follow-up of 8.4 years, have confirmed the benefit of adding pertuzumab to trastuzumab plus chemotherapy in preventing recurrences.
[ccc] Recommendations do not apply to residual DCIS (ypTis).
[ddd] High-risk criteria include stage II–III TNBC. The use of adjuvant pembrolizumab (category 2A) may be individualized.
[eee] There are no data on sequencing or combining adjuvant capecitabine, pembrolizumab and/or olaparib in patients who meet criteria for treatment with one or more of these agents. However, their sequential/combined use may be considered in certain patients with high-risk of recurrence.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE – HER2-POSITIVE DISEASE[d,t,bb]



[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] Principles of Biomarker Testing (BINV-A).
[t] Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[x] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[bb] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus, individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).
[dd] See Adjuvant Endocrine Therapy and Principles of Adjuvant Endocrine Therapy (BINV-K).
[ee] Preoperative/Adjuvant Therapy Regimens (BINV-L).
[ff] The prognosis of patients with pT1a and pT1b tumors that are pN0 is uncertain even when HER2 is amplified or overexpressed. This is a population of patients with breast cancer that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.
[gg] Adjuvant chemotherapy with weekly paclitaxel and trastuzumab can be considered for pT1,N0,M0, HER2-positive cancers, particularly if the primary cancer is HR-negative. The absolute benefit of HER2-based systemic chemotherapy is likely negligible in patients with HR-positive cancers and tumor size bordering on T1mic (<1 mm), when the estimated recurrence risk is less than 5% and endocrine therapy remains a viable option for systemic treatment.
[hh] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[ii] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab is unknown.
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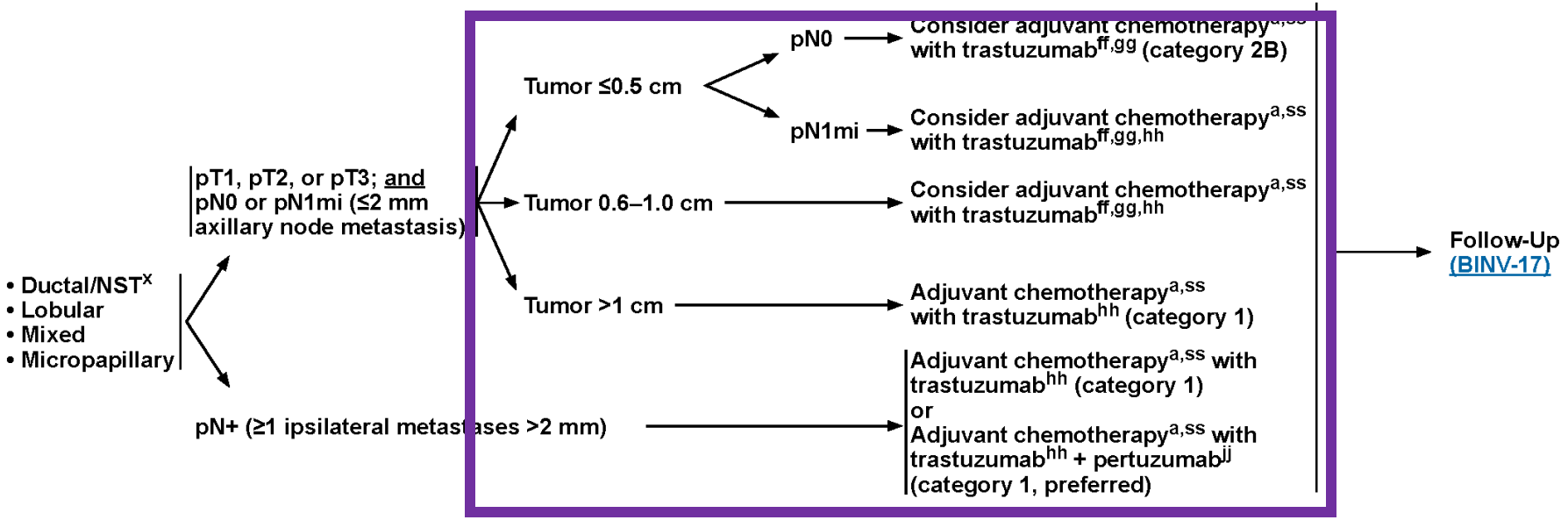
SYSTEMIC ADJUVANT TREATMENT: HR-NEGATIVE – HER2-POSITIVE DISEASE[d,t]



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[d] Principles of Biomarker Testing (BINV-A).
[t] Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[x] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[ff] The prognosis of patients with T1a and T1b tumors that are pN0 is uncertain even when HER2 is amplified or overexpressed. This is a population of patients with breast cancer that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.
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[ss] Preoperative/Adjuvant Therapy Regimens (BINV-L).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CAN ANTHRACYCLINES BE SUBSTITUTED BY TAXANES?

IS ANTHRACYCLINE-BASED CHEMOTHERAPY NECESSARY?

BCIRG006: 10.3 YRS FOLLOW-UP

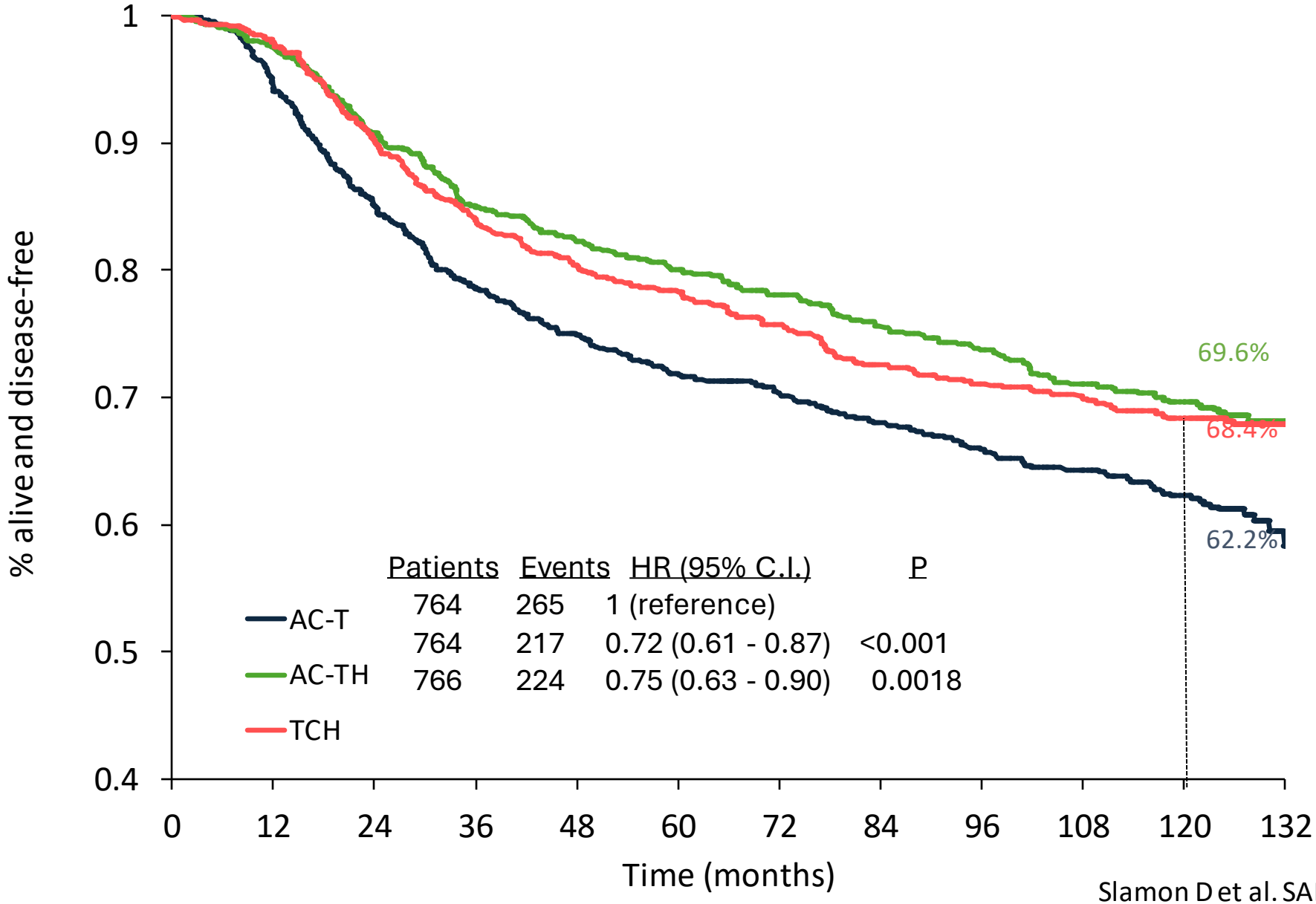
Outcome	AC → T (n = 1073)	AC → TH (n = 1074)	TCH (n = 1075)
DFS, % (n/N) HR (95% CI)	67.9 (328/1073) 1	74.6 (269/1074) 0.72 (0.61-0.85); *P* < .0001	73.0 (279/1075) 0.77 (0.65-0.90); *P* = .0011
OS, % (n/N) HR (95% CI)	78.7 (203/1073) 1	85.9 (141/1074) 0.63 (0.51-0.79); *P* < .0001	83.3 (167/1075) 0.76 (0.62-0.93); *P* = .0075
DFS in LN+ pts, % (n/N) HR (95% CI)	62.2 (265/764) 1	69.6 (217/764) 0.72 (0.61-0.87); *P* < .001	68.4 (224/766) 0.75 (0.63-0.90); *P* = .0018

TCH ASSOCIATED WITH LESS CARDIAC TOXICITY AND NUMERICALLY FEWER CASES OF SECONDARY LEUKEMIA

Slamon D et al. SABCS 2015. Abstract S5-05.

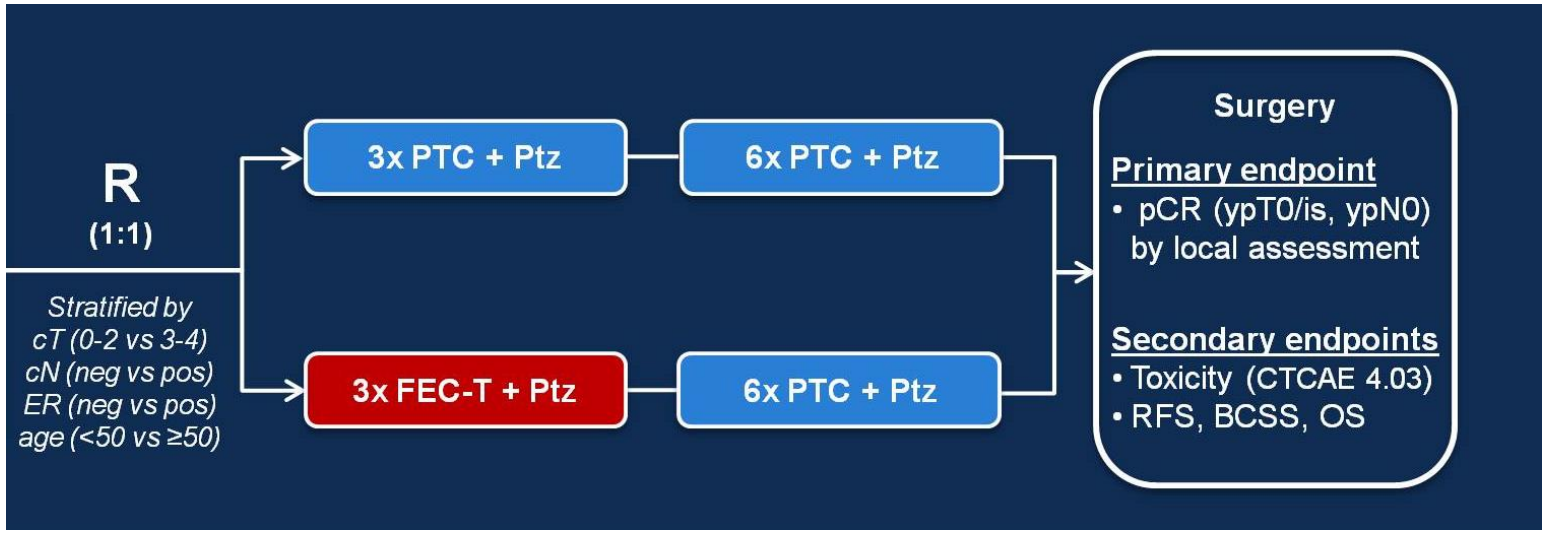
BCIRG 006: DFS LYMPH NODE POSITIVE

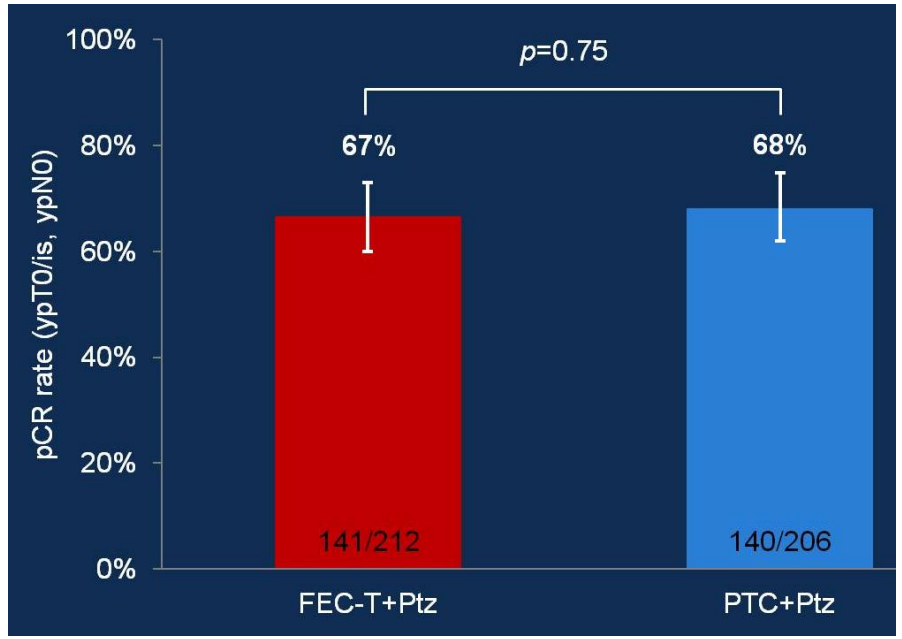
NO ADVANTAGE FOR ANTHRACYCLINES EVEN IN THE HIGH RISK GROUP



Slamon D et al. SABCS 2015. Abstract S5-05.

SUBSTITUTING ANTHRACYCLINE WITH TAXANE: TRAIN-2

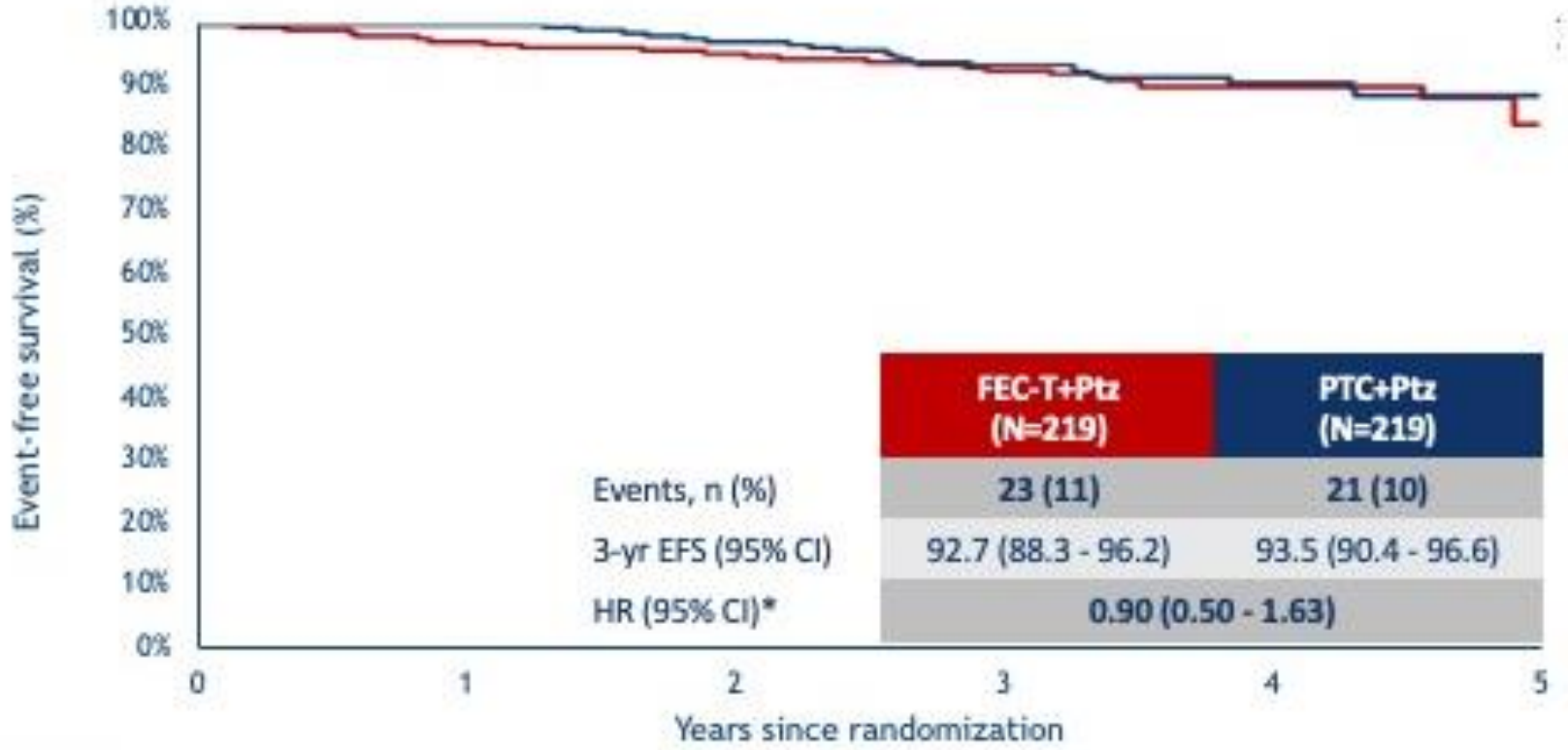




- 64% node positive, 42% HR negative
- pCR was consistent across all subgroups
- More pts completed 1 year trastuzumab in PTC/Ptz arm (97% vs 89%)
- Significantly more grade 3/4 febrile neutropenia (10% vs 1%) in anthracycline arm

Van Ramshorst MS, et al. ASCO 2017. Abstract 507.
Van Ramshorst MS, et al. *Lancet Oncol*. 2018;19(12):1630-1640.

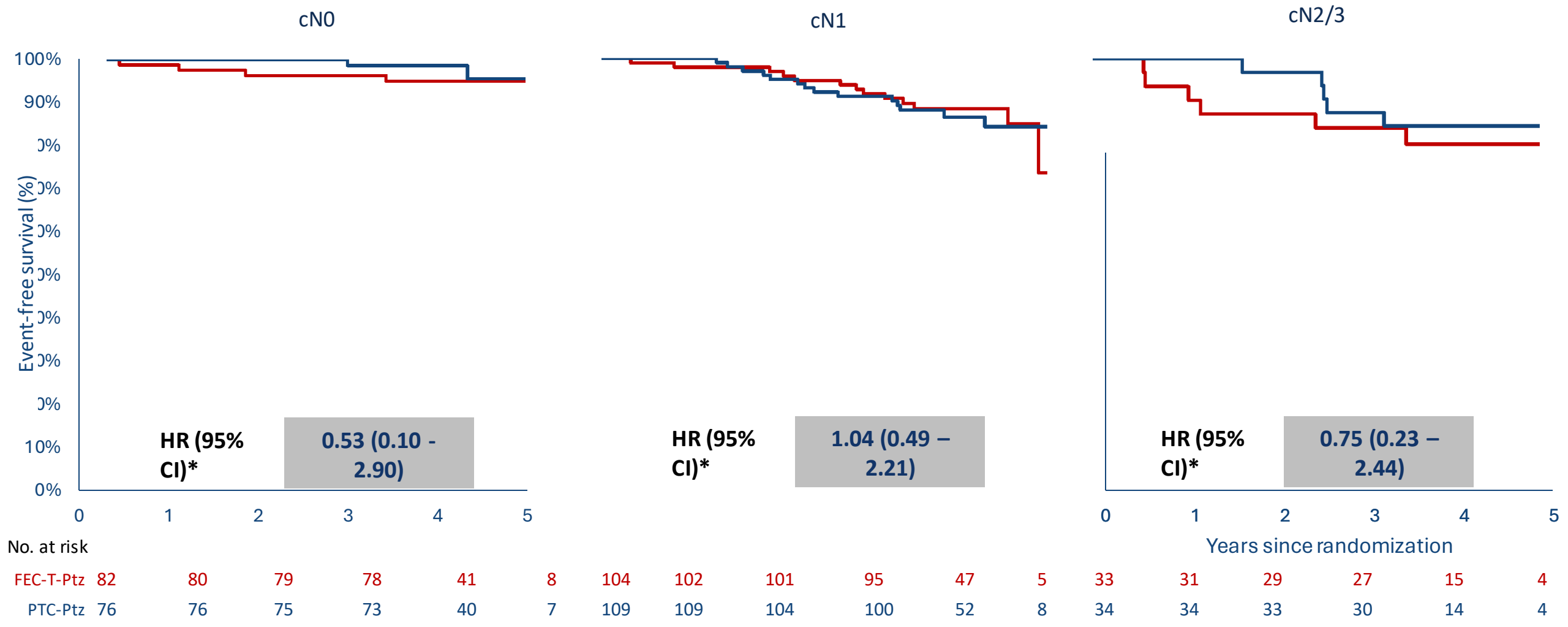
TRAIN-2: EFS



- Significantly less cardiac toxicity PTC+Ptz
- 2 leukemia in FEC-arm

Van der Voort A et al. ASCO 2020. Abstract 501.

EFS TRAIN-2 BY NODAL STATUS



No. at risk

FEC-T-Ptz	82	80	79	78	41	8	104	102	101	95	47	5	33	31	29	27	15	4
PTC-Ptz	76	76	75	73	40	7	109	109	104	100	52	8	34	34	33	30	14	4

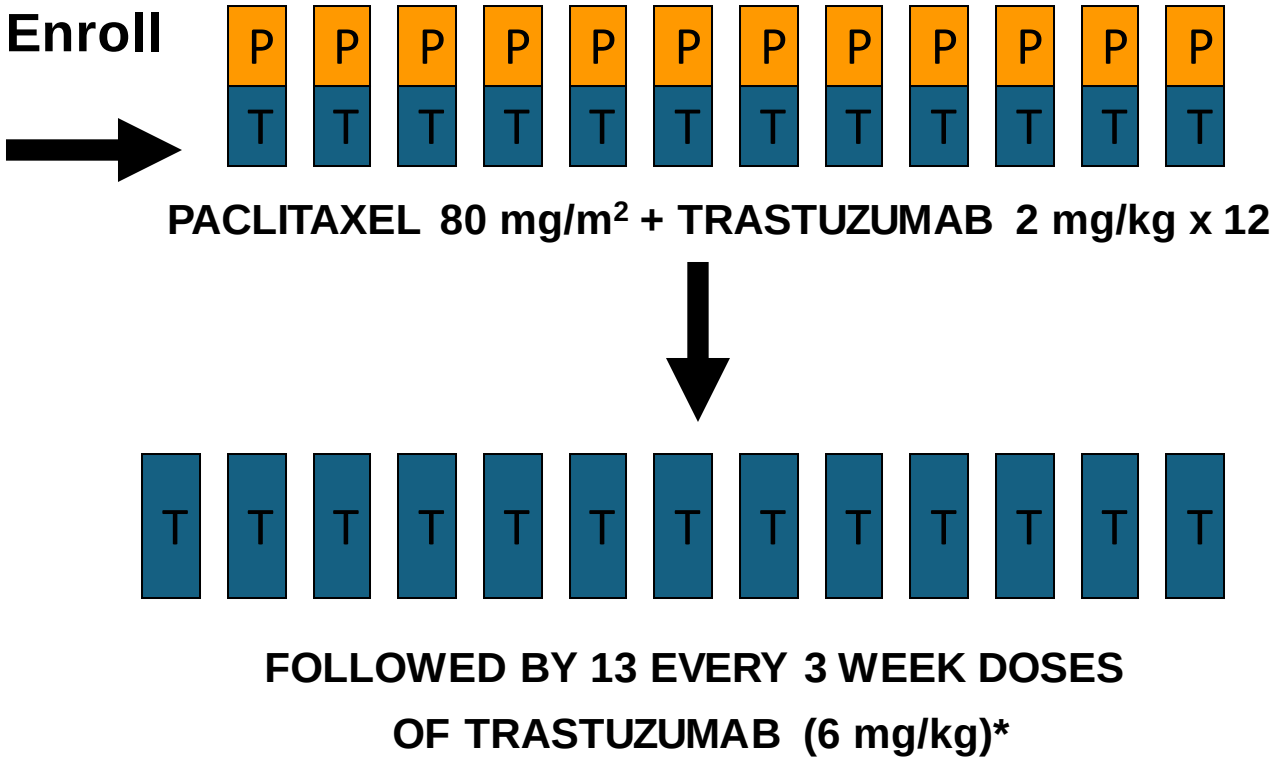
*HR <1 favors PTC+Ptz

Van der Voort A et al. ASCO 2020. Abstract 501.

APT TRIAL: STUDY DESIGN

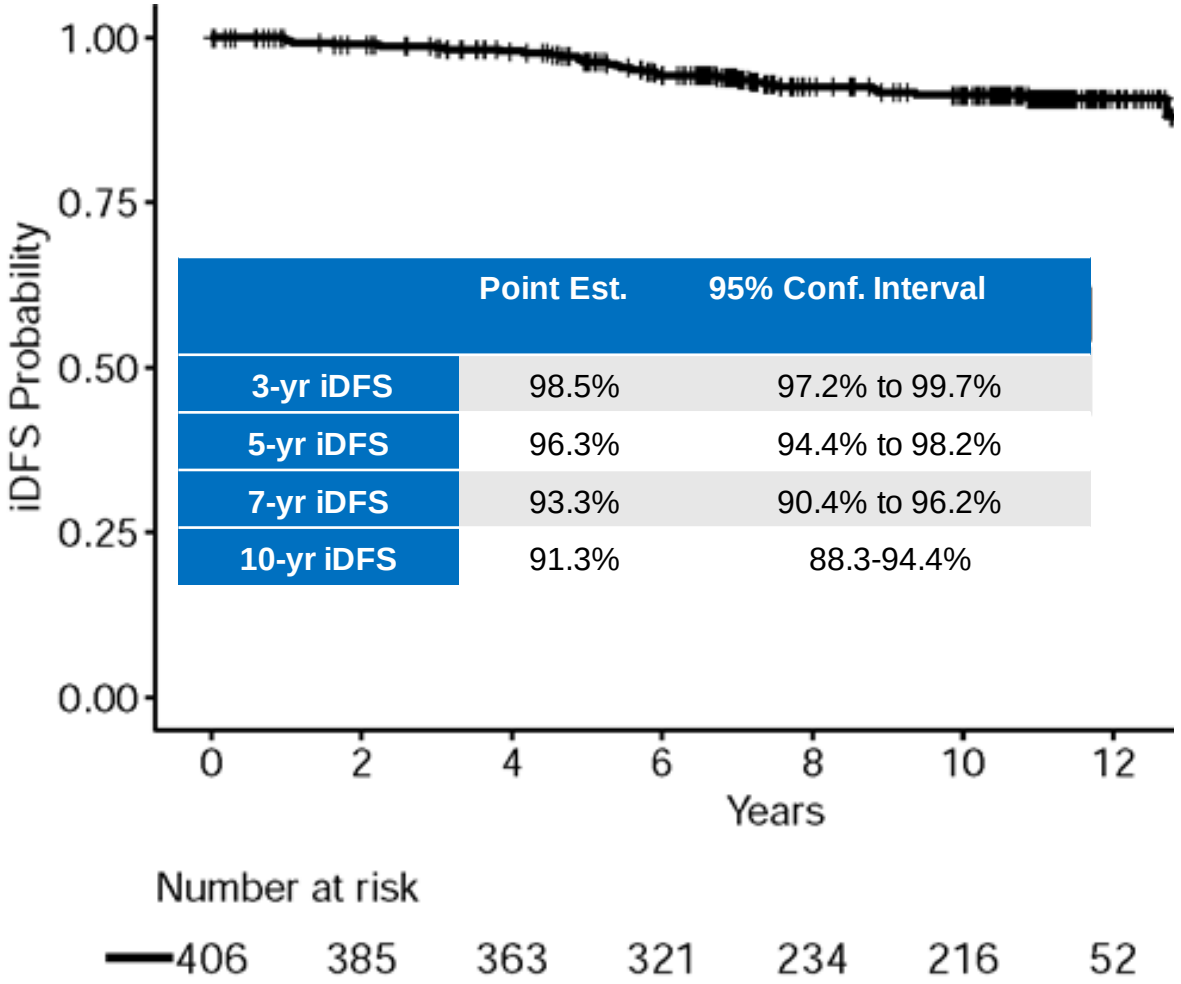
HER2+
ER+ or ER-
Node Negative
≤ 3 cm

Planned N=400



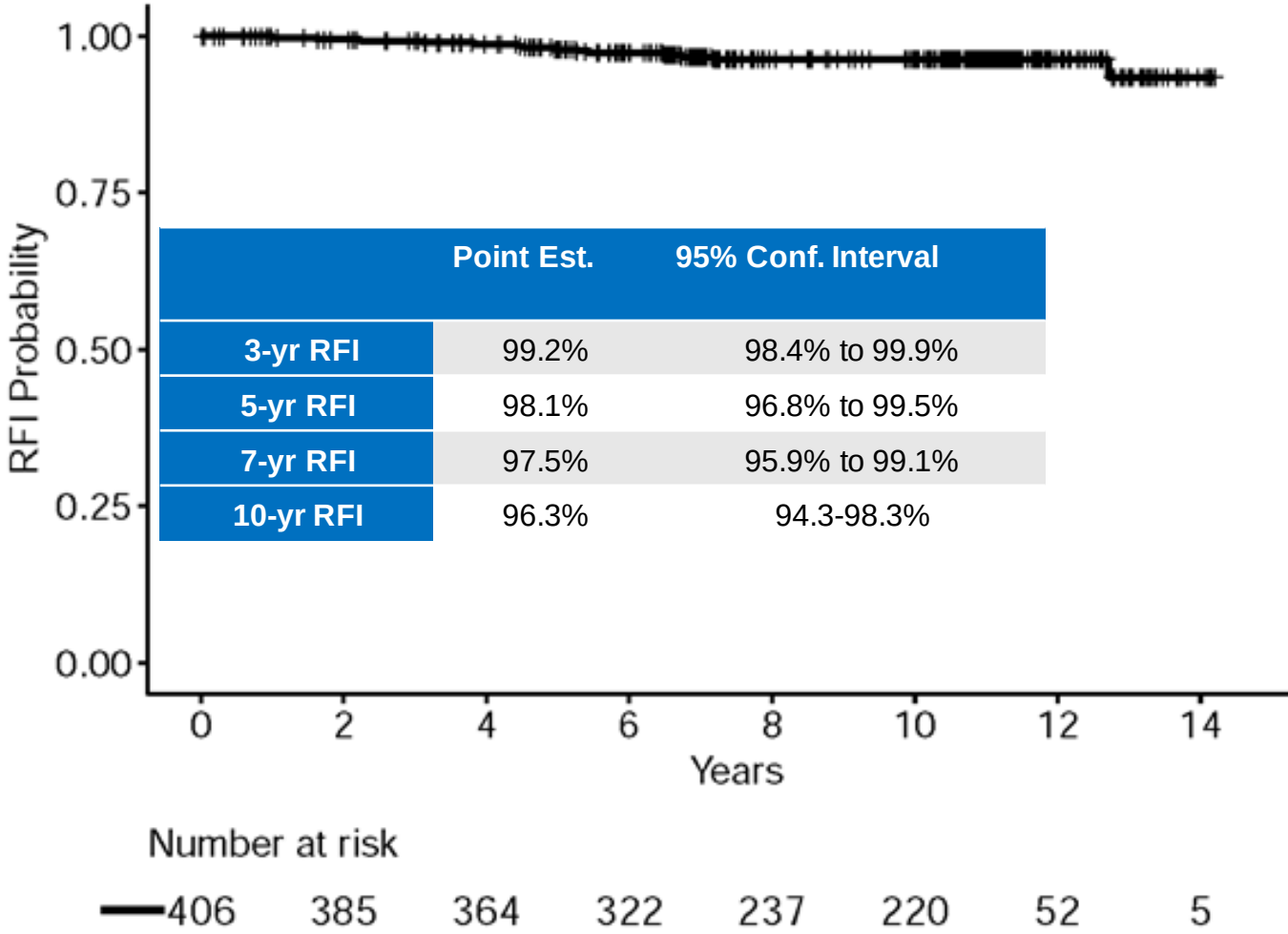
Tolaney SM et al. *N Engl J Med*. 2015;372(2):134-41.
Tolaney SM et al. *J Clin Oncol*. 2019;37(22):1868-1875.

APT: 10 year RESULTS



	Point Est.	95% Conf. Interval
3-yr iDFS	98.5%	97.2% to 99.7%
5-yr iDFS	96.3%	94.4% to 98.2%
7-yr iDFS	93.3%	90.4% to 96.2%
10-yr iDFS	91.3%	88.3-94.4%

6 Distant Events

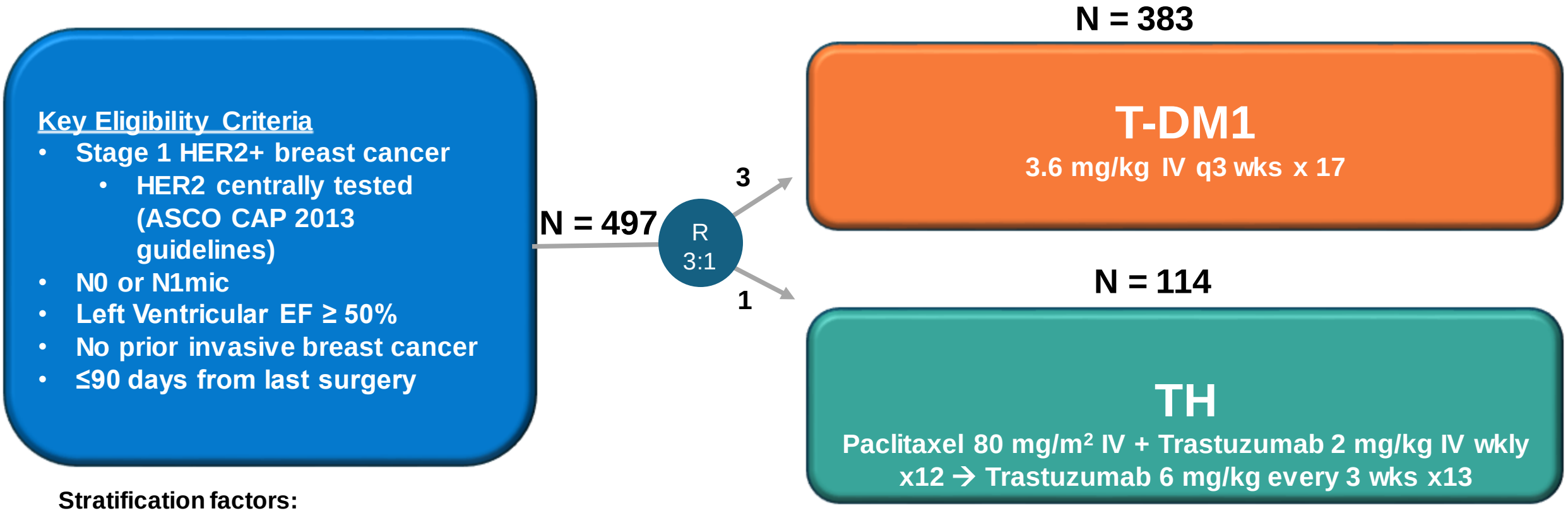


	Point Est.	95% Conf. Interval
3-yr RFI	99.2%	98.4% to 99.9%
5-yr RFI	98.1%	96.8% to 99.5%
7-yr RFI	97.5%	95.9% to 99.1%
10-yr RFI	96.3%	94.3-98.3%

RFI Events=
- **Invasive Local/Regional Recurrence**
- **Distant Recurrence**
- **Death from Breast Cancer**

Tolaney SM et al. SABCS 2022. Abstract PD18-02.
Tolaney SM et al. *Lancet Oncol*. 2023;24(3):273-285.

Does T-DM1 have a role for Stage I HER2+ Disease? ATEMPT Trial



Stratification factors:

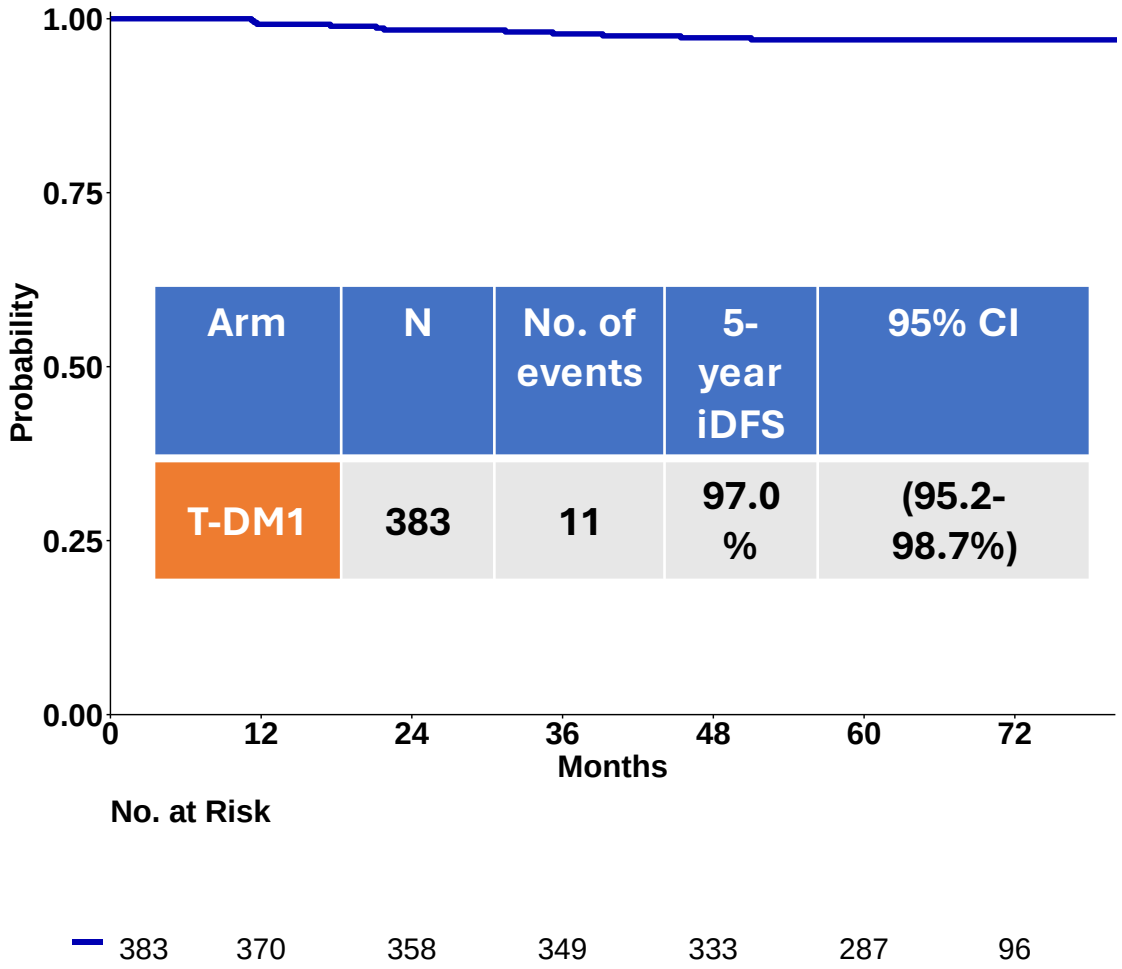
- **Age (<55, ≥55)**
- **Planned radiation (Yes/No)**
- **Planned hormonal therapy (Yes/No)**

***Radiation and endocrine therapy could be initiated after 12 weeks on study therapy**

Tolaney S et al. SABCS 2019. GS1-05.

5-year outcomes with T-DM1: iDFS and RFI

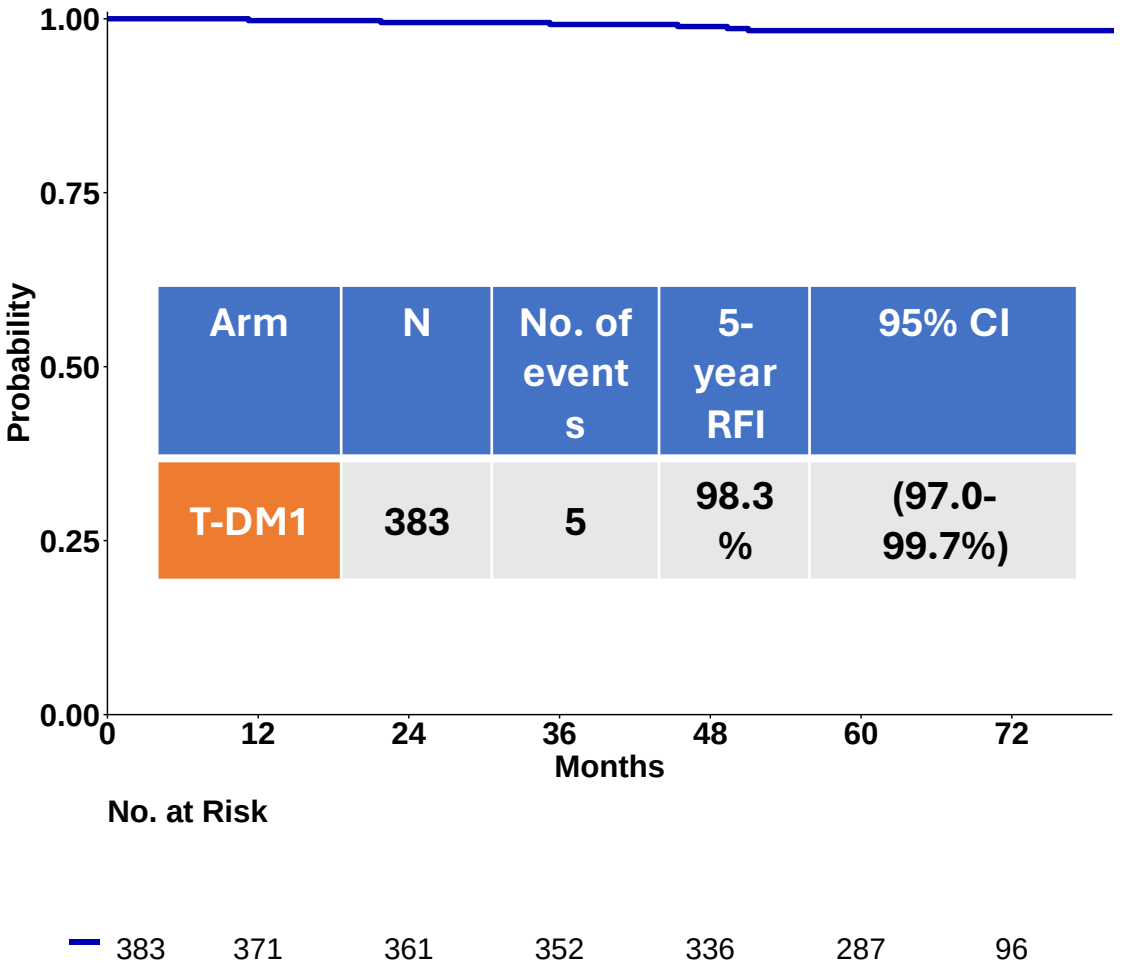
5-year iDFS



Arm	N	No. of events	5-year iDFS	95% CI
T-DM1	383	11	97.0 %	(95.2-98.7%)

3 Distant Events

5-year RFI



Arm	N	No. of events	5-year RFI	95% CI
T-DM1	383	5	98.3 %	(97.0-99.7%)

Tarantino P et al. SABCS 2022. Abstract PD18-01.

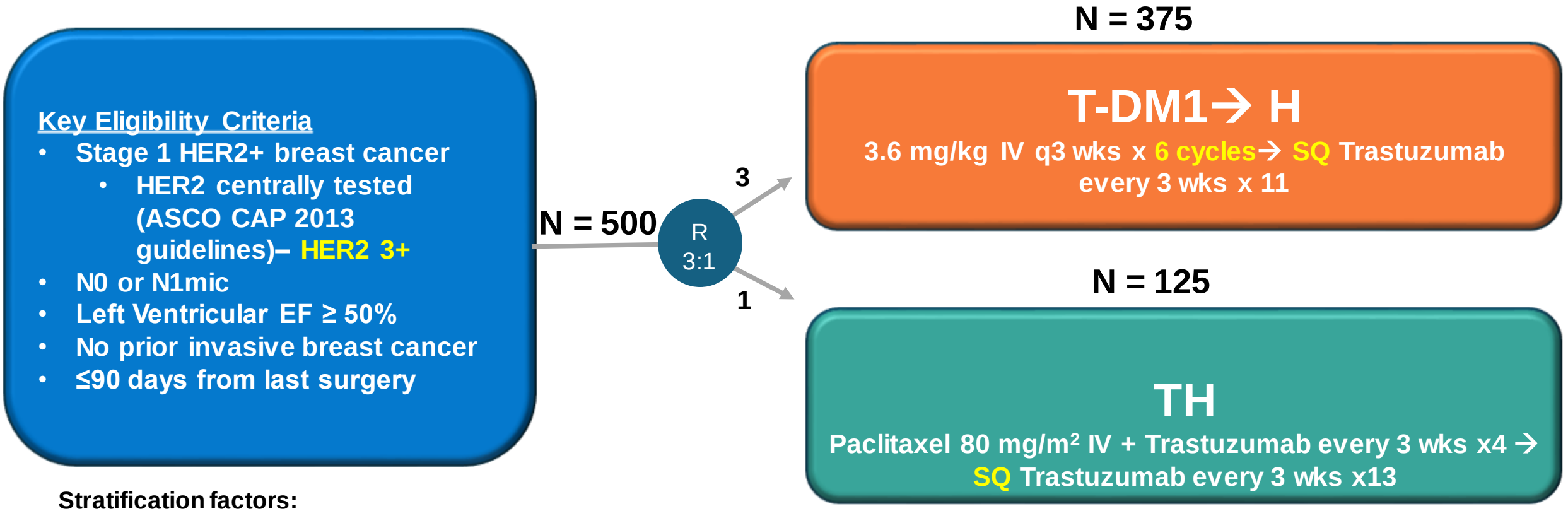
ATEMPT: CLINICALLY RELEVANT TOXICITY

Clinically Relevant Toxicity	T-DM1 (n = 383) N (%)	TH (n = 114) N (%)
Grade ≥3 non-hematologic toxicity	37 (10%)	13 (11%)
Grade ≥ 2 neurotoxicity	42 (11%)	26 (23%)
Grade ≥4 hematologic toxicity	4 (1%)	0 (0%)
Febrile neutropenia	0 (0%)	2 (2%)
Any toxicity requiring dose delay	106 (28%)	30 (26%)
Any toxicity requiring early discontinuation	67 (17%)	7 (6%)
Total	176 (46%)	53 (46%)

p=0.91

Tolaney S et al. SABCS 2019. GS1-05.

ONGOING STUDY: ATEMPT 2.0



Stratification factors:

- **Age (<55, ≥55)**
- **Planned radiation (Yes/No)**
- **Planned hormonal therapy (Yes/No)**

***Radiation and endocrine therapy could be initiated after 12 weeks on study therapy**

PI: Sara Tolaney

Non-Inferiority RCTs of trastuzumab duration

Trial	Duration	Patients
PERSEPHONE	12m v 6m	4088
PHARE	12m v 6m	3380
HORG	12m v 6m	493
Subtotal	**7,961**	
SOLD	12m v 9w	2174
Shorther	12m v 9w	1254
Subtotal	**3428**	
TOTAL		**11,389**

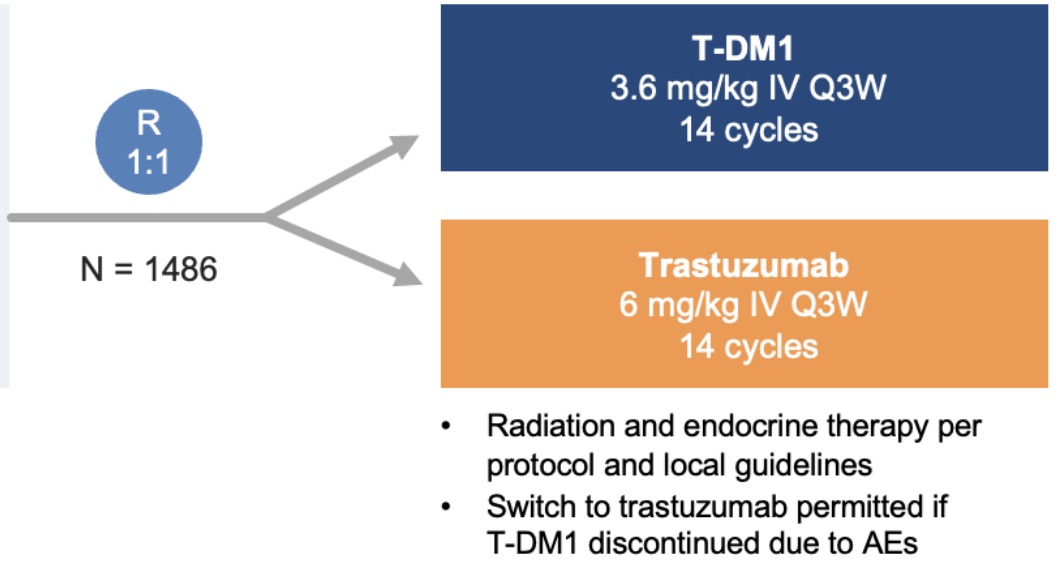
Earl H et al. ESMO 2021. Abstract LBA11.

Can we give less than 1 year of trastuzumab?

- Only regimen where one year of trastuzumab alone is given currently is with paclitaxel + trastuzumab
    - No data with less intensive chemotherapy that we can do shorter duration trastuzumab
- Modern era regimens use dual HER2-directed therapy in stage 2/3 breast cancer, and T-DM1 in patients with residual disease, so these data are not applicable with these regimens
- 1 year remains the standard
    - More work needed for stage 1 patients to see if shorter duration therapy would be equally efficacious
    - Work needed in patients who achieve pCR to standard regimens to know if a full year of HER2-directed therapy is really needed

KATHERINE Study Update

- Prior neoadjuvant therapy consisting of:
  - Minimum 6 cycles of chemotherapy
  - Minimum 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



- Radiation and endocrine therapy per protocol and local guidelines
- Switch to trastuzumab permitted if T-DM1 discontinued due to AEs

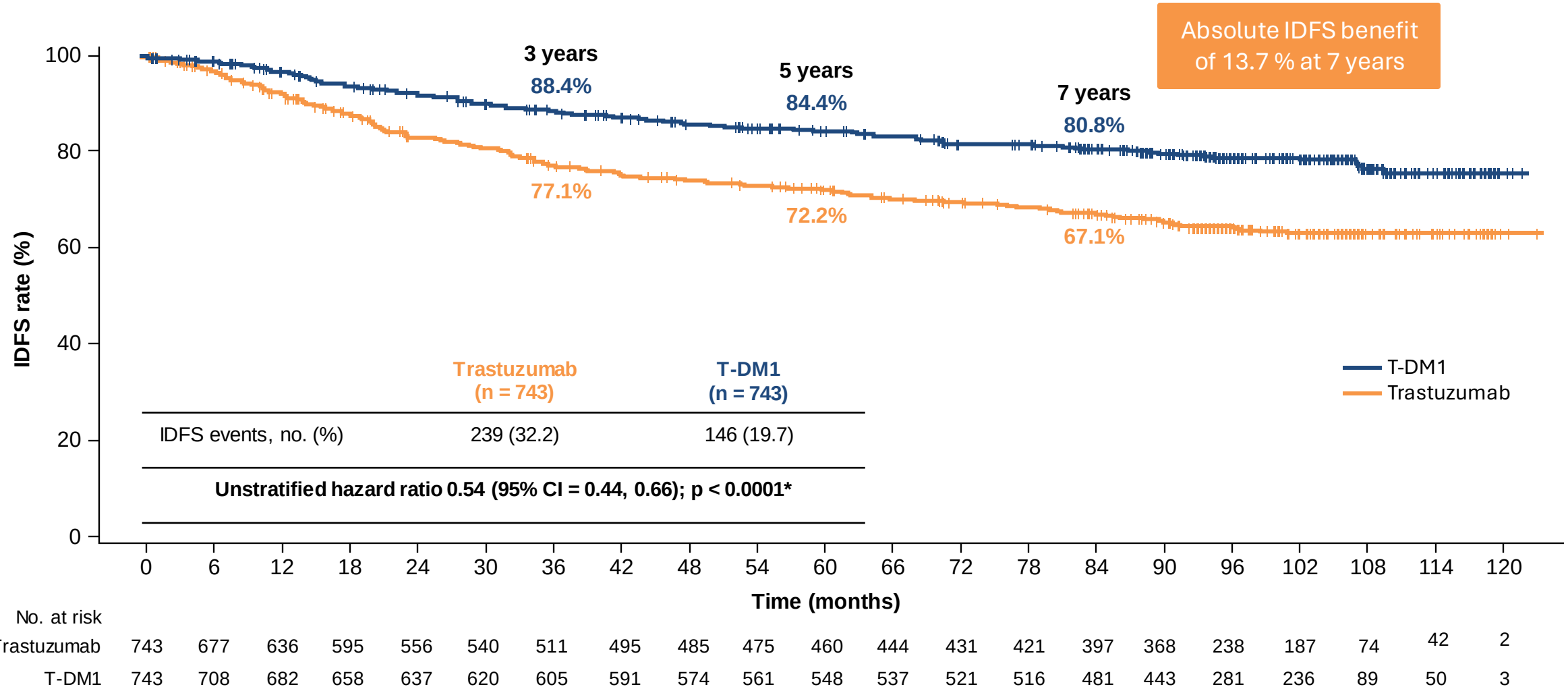
- **Primary endpoint:** IDFS
- **Secondary endpoints:** IDFS with second primary non-breast cancers included, DFS, OS, DRFI, safety, and QoL
- **Stratification factors:** Clinical stage at presentation (inoperable vs operable), HR status, preoperative HER2-directed therapy, pathologic nodal status after preoperative therapy

AE, adverse event; DFS, disease-free survival; DRFI, distant recurrence-free interval; HR, hormone receptor; IDFS, invasive disease-free survival; IV, intravenous; OS, overall survival; Q3W, every 3 weeks; QoL, quality of life; R, randomized; T-DM1, ado-trastuzumab emtansine.

Adapted from *N Engl J Med*, von Minckwitz *et al.*, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, Vol. 380, Pages 617–628.

Loibl et al, SABCS 2023

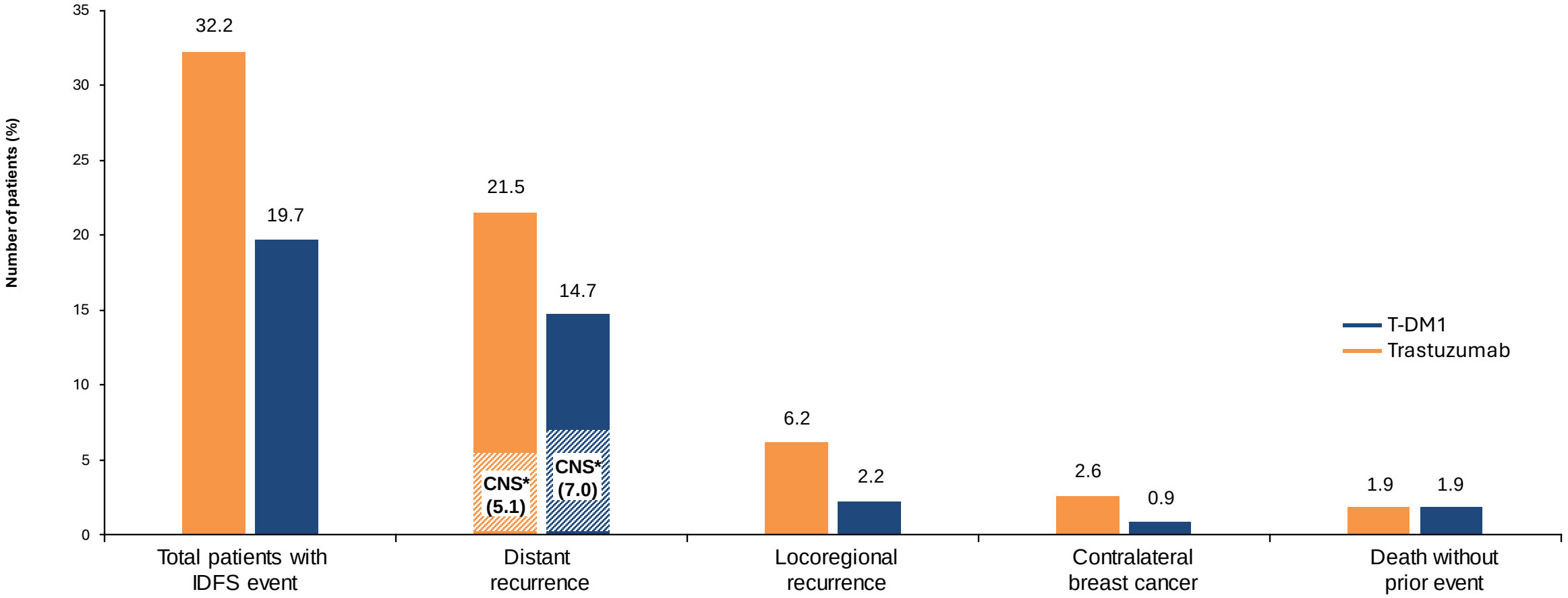
KATHERINE IDFS final analysis; median follow-up 8.4 years



* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Loibl et al, SABCS 2023

Site of first occurrence of an IDFS event

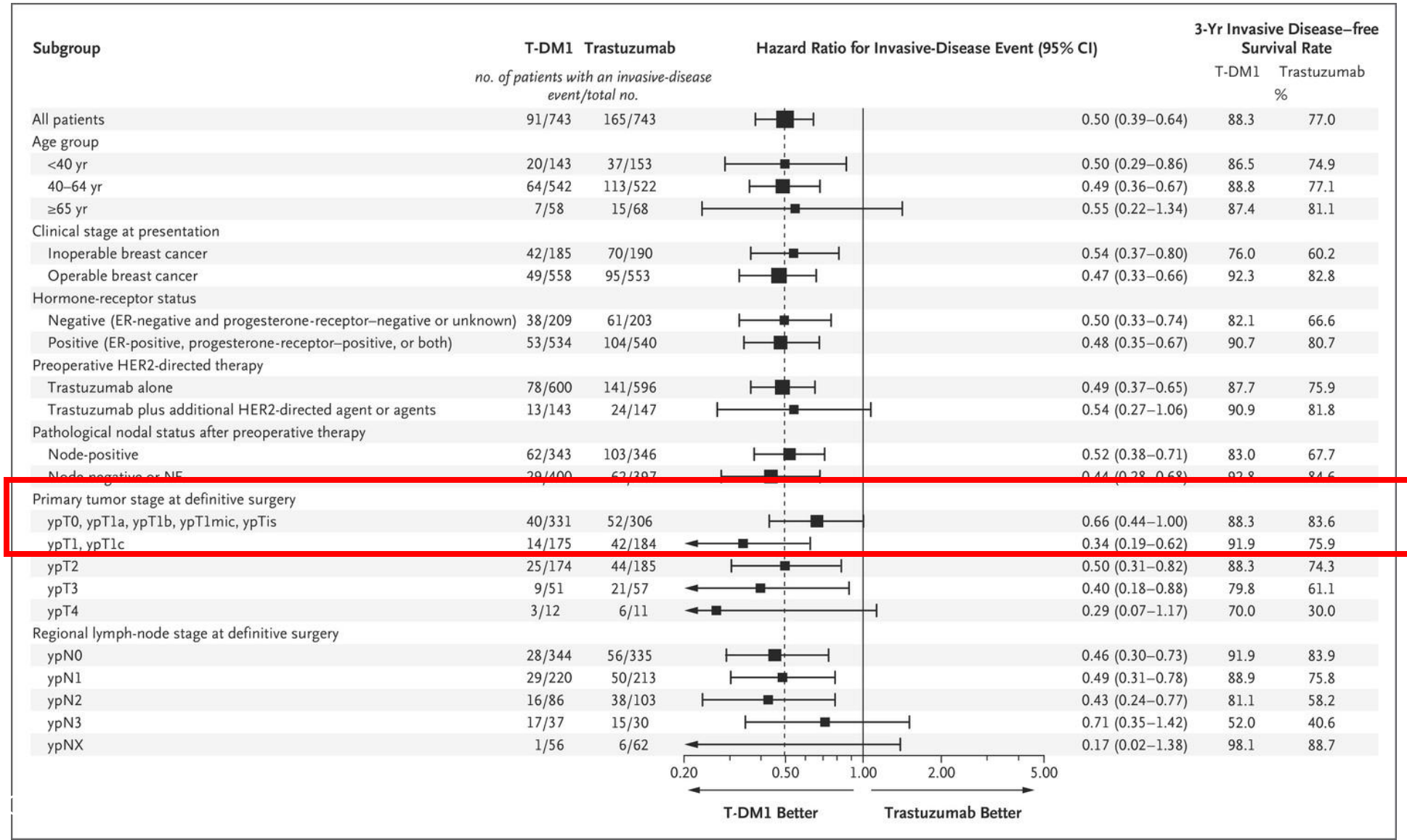


* **CNS metastases as component of distant recurrence (isolated or with other sites).** Trastuzumab T-DM1
CNS recurrence after first IDFS event: 19 patients (2.6%) in the trastuzumab arm and four patients (0.5%) in the T-DM1 arm.
CNS, central nervous system; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Loibl et al, SABCS 2023

KATHERINE:

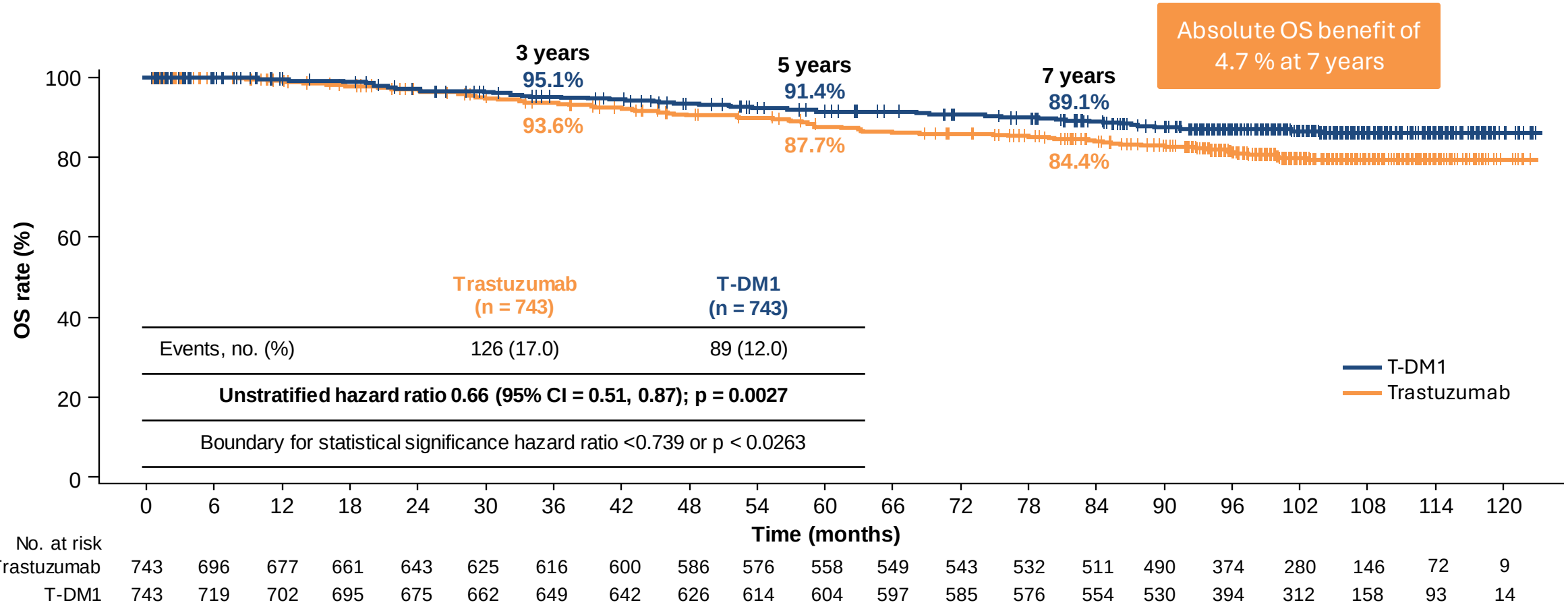
All patients benefit even those with small amounts of residual tumor



Subgroup	T-DM1	Trastuzumab	Hazard Ratio for Invasive-Disease Event (95% CI)	3-Yr Invasive Disease–free Survival Rate	
	no. of patients with an invasive-disease event/total no.			T-DM1 %	Trastuzumab %
All patients	91/743	165/743	0.50 (0.39–0.64)	88.3	77.0
Age group					
<40 yr	20/143	37/153	0.50 (0.29–0.86)	86.5	74.9
40–64 yr	64/542	113/522	0.49 (0.36–0.67)	88.8	77.1
≥65 yr	7/58	15/68	0.55 (0.22–1.34)	87.4	81.1
Clinical stage at presentation					
Inoperable breast cancer	42/185	70/190	0.54 (0.37–0.80)	76.0	60.2
Operable breast cancer	49/558	95/553	0.47 (0.33–0.66)	92.3	82.8
Hormone-receptor status					
Negative (ER-negative and progesterone-receptor–negative or unknown)	38/209	61/203	0.50 (0.33–0.74)	82.1	66.6
Positive (ER-positive, progesterone-receptor–positive, or both)	53/534	104/540	0.48 (0.35–0.67)	90.7	80.7
Preoperative HER2-directed therapy					
Trastuzumab alone	78/600	141/596	0.49 (0.37–0.65)	87.7	75.9
Trastuzumab plus additional HER2-directed agent or agents	13/143	24/147	0.54 (0.27–1.06)	90.9	81.8
Pathological nodal status after preoperative therapy					
Node-positive	62/343	103/346	0.52 (0.38–0.71)	83.0	67.7
Node-negative or NE	29/400	62/397	0.44 (0.28–0.68)	92.8	84.6
Primary tumor stage at definitive surgery					
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	40/331	52/306	0.66 (0.44–1.00)	88.3	83.6
ypT1, ypT1c	14/175	42/184	0.34 (0.19–0.62)	91.9	75.9
ypT2	25/174	44/185	0.50 (0.31–0.82)	88.3	74.3
ypT3	9/51	21/57	0.40 (0.18–0.88)	79.8	61.1
ypT4	3/12	6/11	0.29 (0.07–1.17)	70.0	30.0
Regional lymph-node stage at definitive surgery					
ypN0	28/344	56/335	0.46 (0.30–0.73)	91.9	83.9
ypN1	29/220	50/213	0.49 (0.31–0.78)	88.9	75.8
ypN2	16/86	38/103	0.43 (0.24–0.77)	81.1	58.2
ypN3	17/37	15/30	0.71 (0.35–1.42)	52.0	40.6
ypNX	1/56	6/62	0.17 (0.02–1.38)	98.1	88.7

Loibl S, et al. ESMO Breast 2020

KATHERINE OS at median follow-up 8.4 years

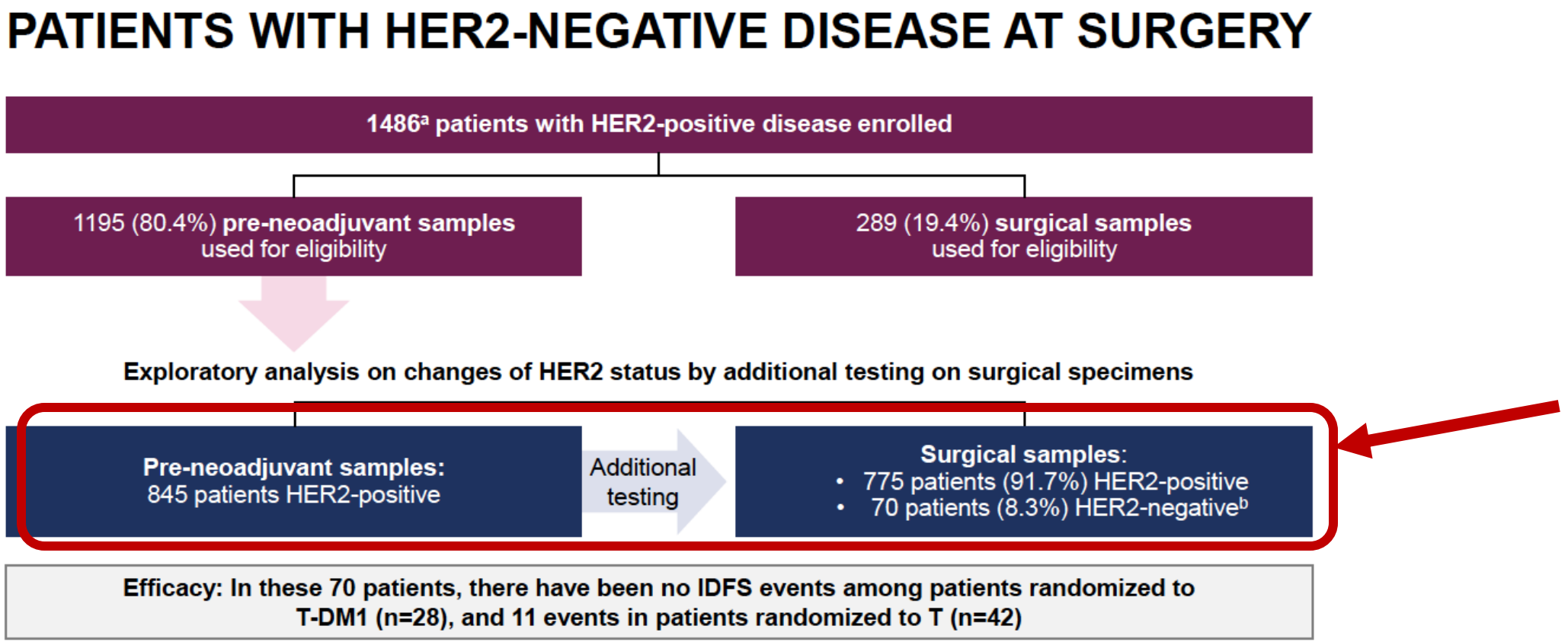


Significant reduction in risk of death by 34% with T-DM1

CI, confidence interval; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

Loibl et al, SABCS 2023

KATHERINE:
What about those with HER2- residual disease?



TREAT PATIENTS WITH HER2+ PRIMARY TUMORS WITH ADJUVANT T-DM1 EVEN IF RESIDUAL DISEASE IS HER2-NEGATIVE

Loibl S, et al. ESMO Breast 2020.

CAN WE IMPROVE UPON KATHERINE?

- 3 yr iDFS for N+ pts: 83%.
- No improvement in rates of CNS recurrence
- May want to consider further treatment escalation with future studies:
  - Add on strategies: T-DM1 + tucatinib
  - Substitution strategies: Trastuzumab deruxtecan

COMPASSHER2 TRIALS

Preoperative Phase: all patients

Eligibility:
Stage II or IIIA HER2+ BC (T2-3, N0-2)

- cN0 eligible if ≥ 2.0 cm
- cN1-2 eligible ≥ 1.5cm
- ER+ and ER- eligible

REGISTRATION

THP x 4 Cycles
Paclitaxel qwk x12
OR
Docetaxel q3 wk x4
with
Trastuzumab (H)
& Pertuzumab (P) q3 wk x4

* nab-pacl allowed

SURGERY

pCR (ypT0/Tis ypN0) *40%*

No pCR *60%*

Arm A: pCR (no invasive disease)

EA1181
CompassHER2-pCR

- Complete 1 yr HP
- Radiation and endocrine Rx (if appropriate)

ECOG-ACRIN cancer research group
Reshaping the future of patient care

A011801
CompassHER2-RD

Alliance for Clinical Trials in Oncology

Grp 1: pre-op THP-> AC, Cb/HP x 4
Grp 2: pre-op TCHP, *AC-THP* -> no further chemo

Eligibility
HER2+ RD
ER- & ER+
(ER+ must be N+)
(~30% of A011801 expected to come from EA1181)

Registration

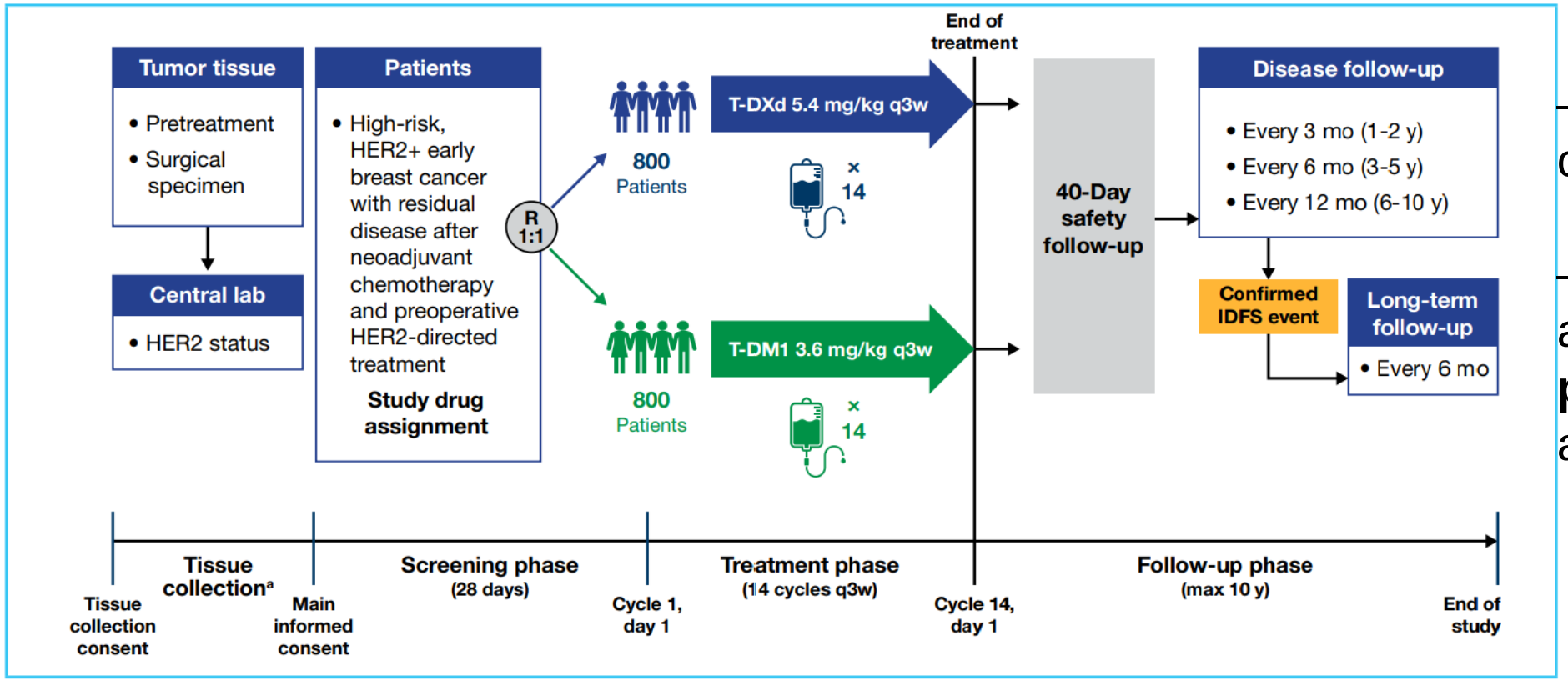
R

T-DM1 x 14 doses

T-DM1/tucatinib x 14 doses

DESTINY-Breast05 phase 3 trial

DESTINY-Breast05: A Multicenter, Open-Label, Randomized Phase 3 Trial Comparing the Efficacy and Safety of T-DXd vs T-DM1 in High-Risk Patients With HER2-Positive, Residual, Invasive Breast Cancer After Neoadjuvant Therapy (N≈1600)



HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; lab, laboratory; max, maximum; q3w, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a] Patients may move into the main screening phase before HER2 status results are available from the central laboratory.

– **Inoperable** breast cancer at presentation

– Operable breast cancer at presentation with **node–positive (ypN1-3) disease** after neoadjuvant therapy

Geyer et al. SABCS 2020. Abstract OT-03-01.

Escalation based on clinical risk: DESTINY-Breast11 Trial

Population

HER2+ EBC

HR+ or HR-

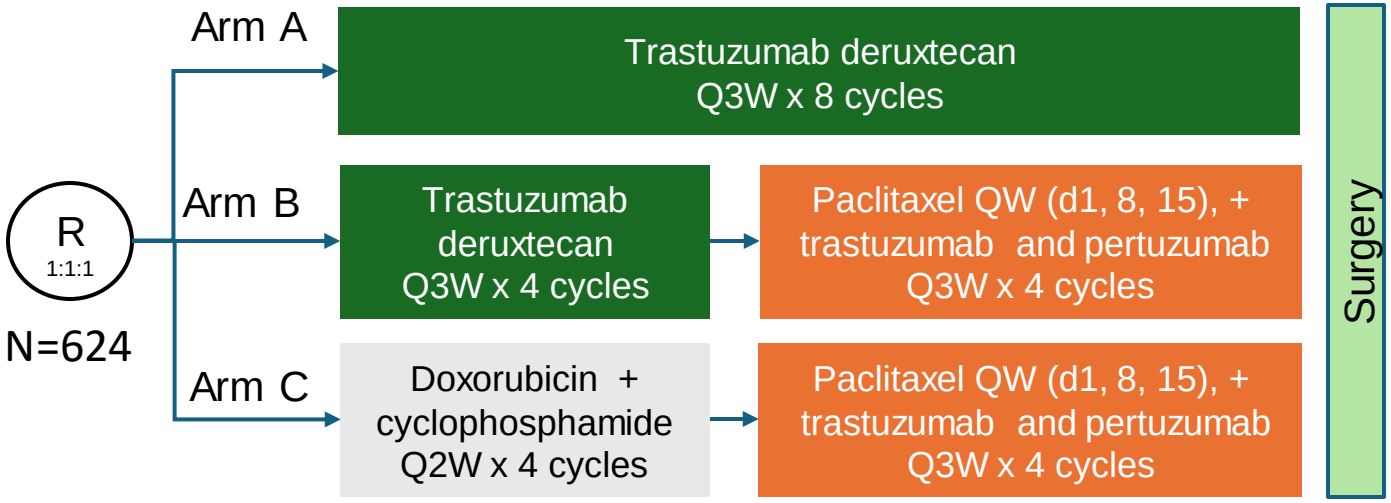
High-risk defined as one of the following:

- $T_xN_{1-3}M_0$
- $T_{3-4}N_xM_0$
- Inflammatory BC

Stratification factors:

- HR Status
  - HR+ vs HR-
- HER2 IHC
  - IHC3+ vs Other

Study Design



Endpoints

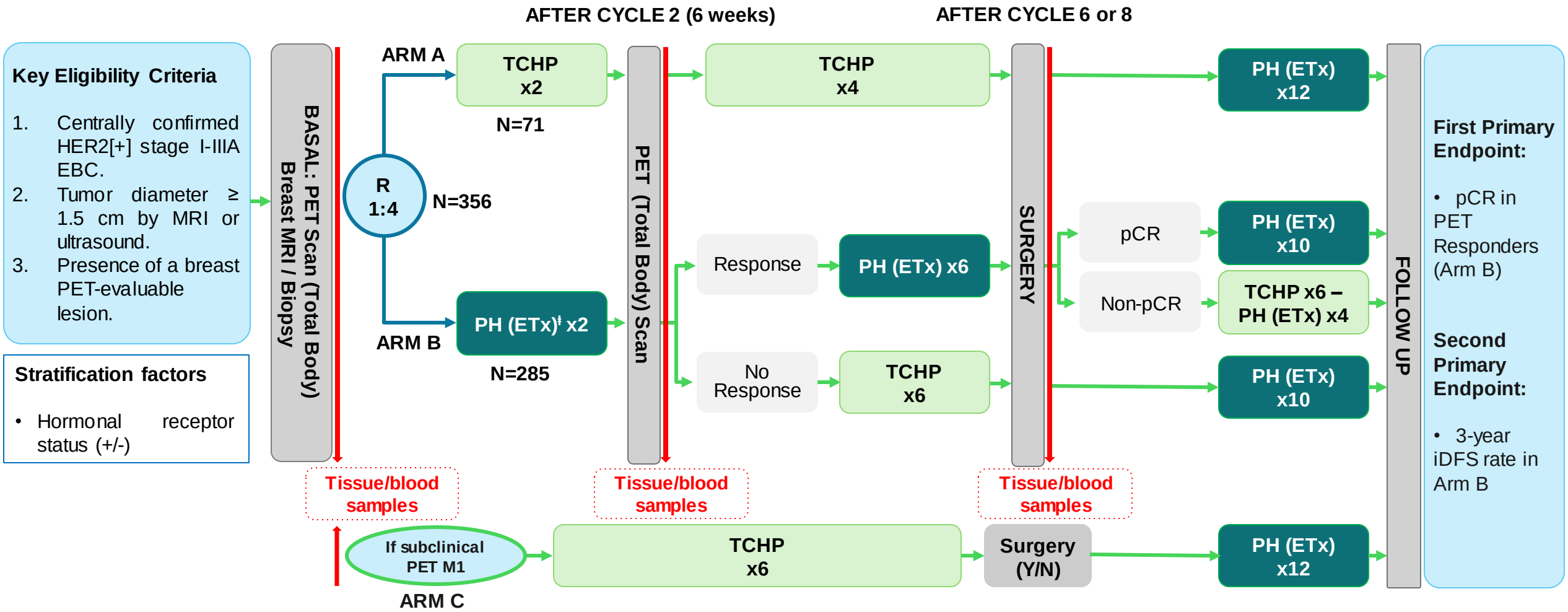
Primary Endpoint:

- pCR (ypT0/Tis ypN0)

Secondary Endpoints:

- pCR (ypT0 ypN0)
- EFS
- IDFS
- OS
- HRQoL
- Safety
- PK and immunogenicity

PHERGAIN Study Design



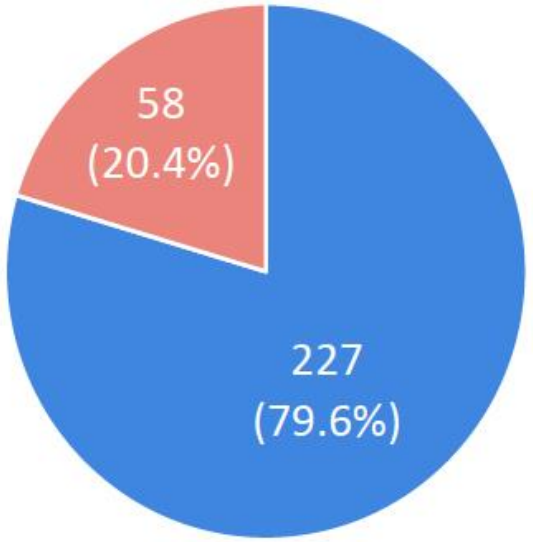
C: Carboplatin; D: Docetaxel; EBC: Early breast cancer; ETx: Endocrine therapy (letrozole post-menopausal/tamoxifen pre-menopausal) Adjuvant ETx up to 3 years from surgery; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; H: Trastuzumab SC; HER2: Human Epidermal Growth Factor Receptor 2; iDFS: Invasive disease-free survival; MRI: Magnetic resonance Imaging; P: Pertuzumab IV; R: Randomization; TCHP: Trastuzumab, pertuzumab, docetaxel, and carboplatin. ‡ All hormonal receptor-positive patients will receive ETx concomitantly with PH (except on chemotherapy).

- PET RESPONDERS: RECIST responders after cycle 2 with SUV_{max} reduction ≥40%.
- pCR, Pathological complete response (ypT0/isN0).

Cortes J, et al ASCO 2023

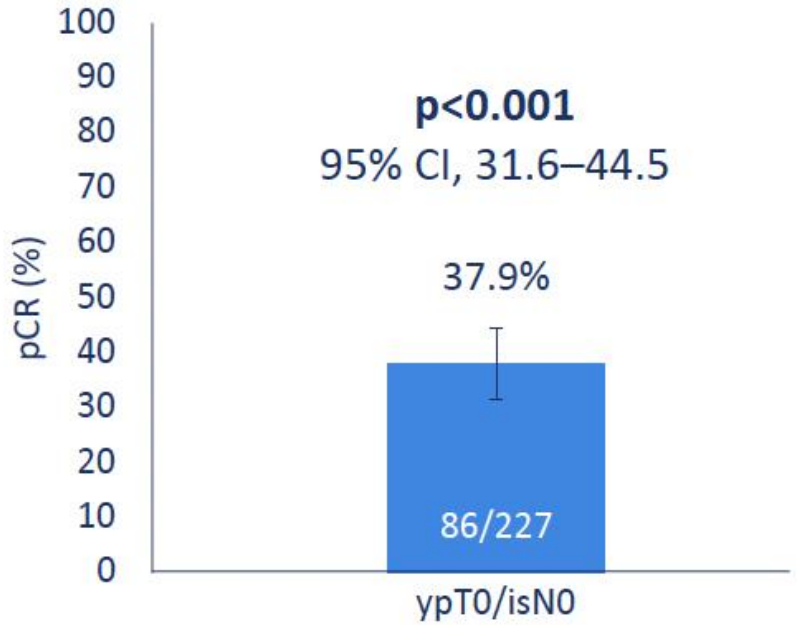
Primary Endpoint: pCR in ^{18}F-FDG-PET responders in group B

PET Responders and Non-Responders



PET Responder PET Non-Responder

pCR rate



Null hypothesis: pCR ≤20%

pCR was observed in patients with both HER2++ and HER2+++, pts with stage II and stage III, and pts ER+ and ER-.

Pérez-García, JM, et al. (2021). *Lancet Oncol*, 22(6), 858-871.

CI: Confidence interval; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response (ypT0/isN0).

Phergain: Efficacy Analysis- Summary of other efficacy endpoints

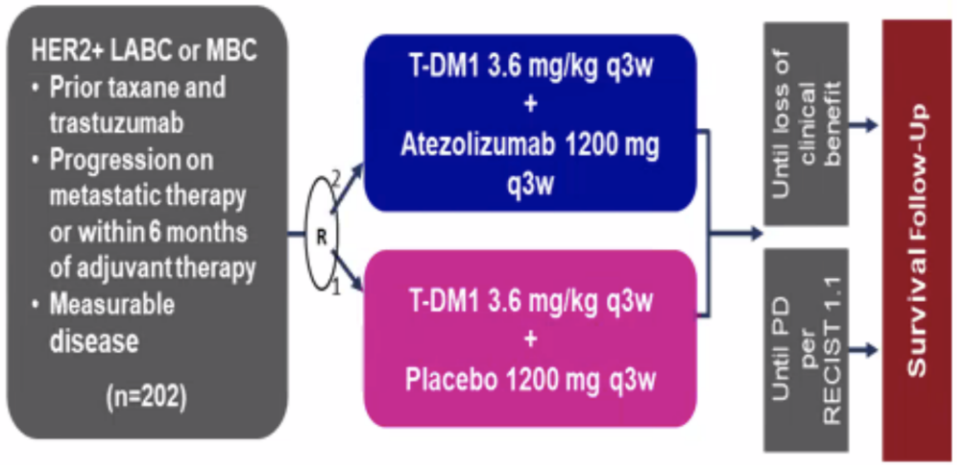
	Group A (n = 63)	Group B (n = 267)	Group B without CT (n = 86)
3-year iDFS	**98.3%**	**95.4%**	**98.8%**
(95% CI)	(95.1–100%)	(92.8–98.0%)	(96.3–100%)
3-year DDFS	**98.3%**	**96.5%**	**100%**
(95% CI)	(95.1–100%)	(94.3–98.8%)	(100–100%)
	(n = 71)	**(n = 285)**	**(n = 86)**
3-year EFS	**98.4%**	**93.5%**	**98.8%**
(95% CI)	(95.3–100%)	(90.7–96.5%)	(96.6–100%)
3-year OS	**98.4%**	**98.5%**	**100%**
(95% CI)	(95.3–100%)	(97.1–100%)	(100–100%)

None of these comparisons between the groups reached statistical significance.
iDFS and DDFS are defined from the time of surgery; EFS and OS are defined from randomization.

Cortes J et al. ASCO 2023. Abstract LBA506.

IMMUNOTHERAPY IN HER2+ MBC: KATE2

Clinical Trial Designs



Stratification factors:

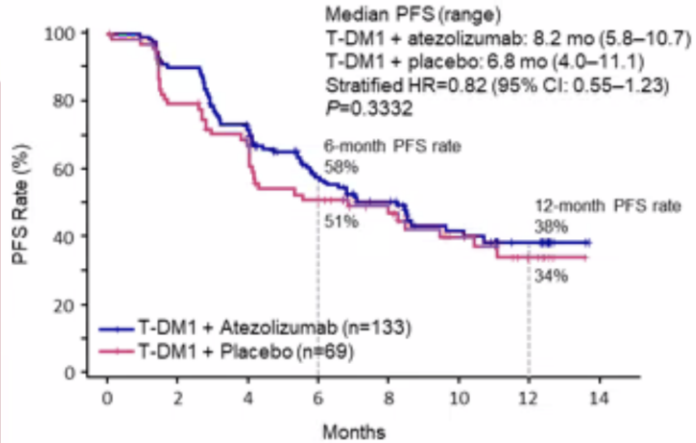
- Tumour PD-L1 IC status (IC0 [<1%] vs IC1/2/3 [≥1%])[a]
- World region (Western Europe vs North America vs rest of world)
- Presence of liver metastases (yes or no)

Primary endpoint:

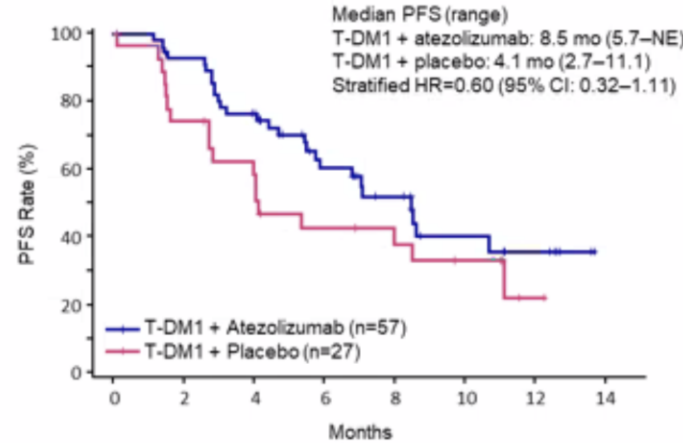
- Investigator-assessed PFS

PFS

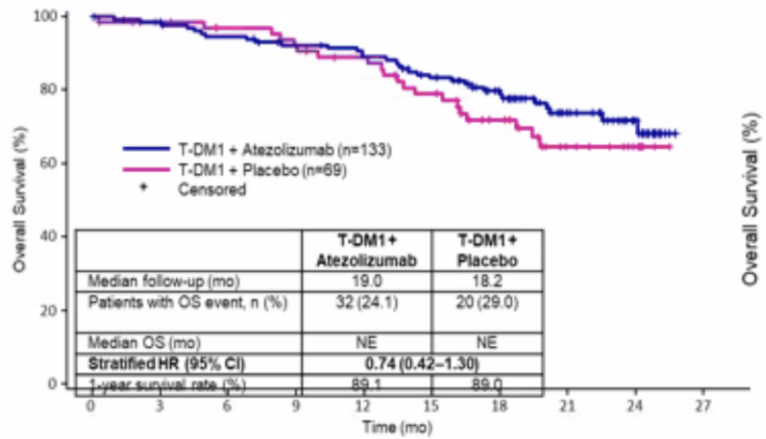
ITT



PD-L1 IC+

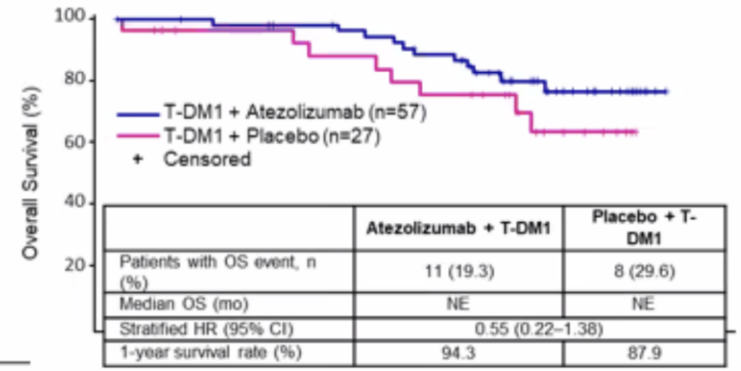


OS



	T-DM1 + Atezolizumab	T-DM1 + Placebo
Median follow-up (mo)	19.0	18.2
Patients with OS event, n (%)	32 (24.1)	20 (29.0)
Median OS (mo)	NE	NE
Stratified HR (95% CI)	0.74 (0.42–1.30)	
1-year survival rate (%)	89.1	89.0

OS in PD-L1 IC+ Subgroup (IC 1/2/3)

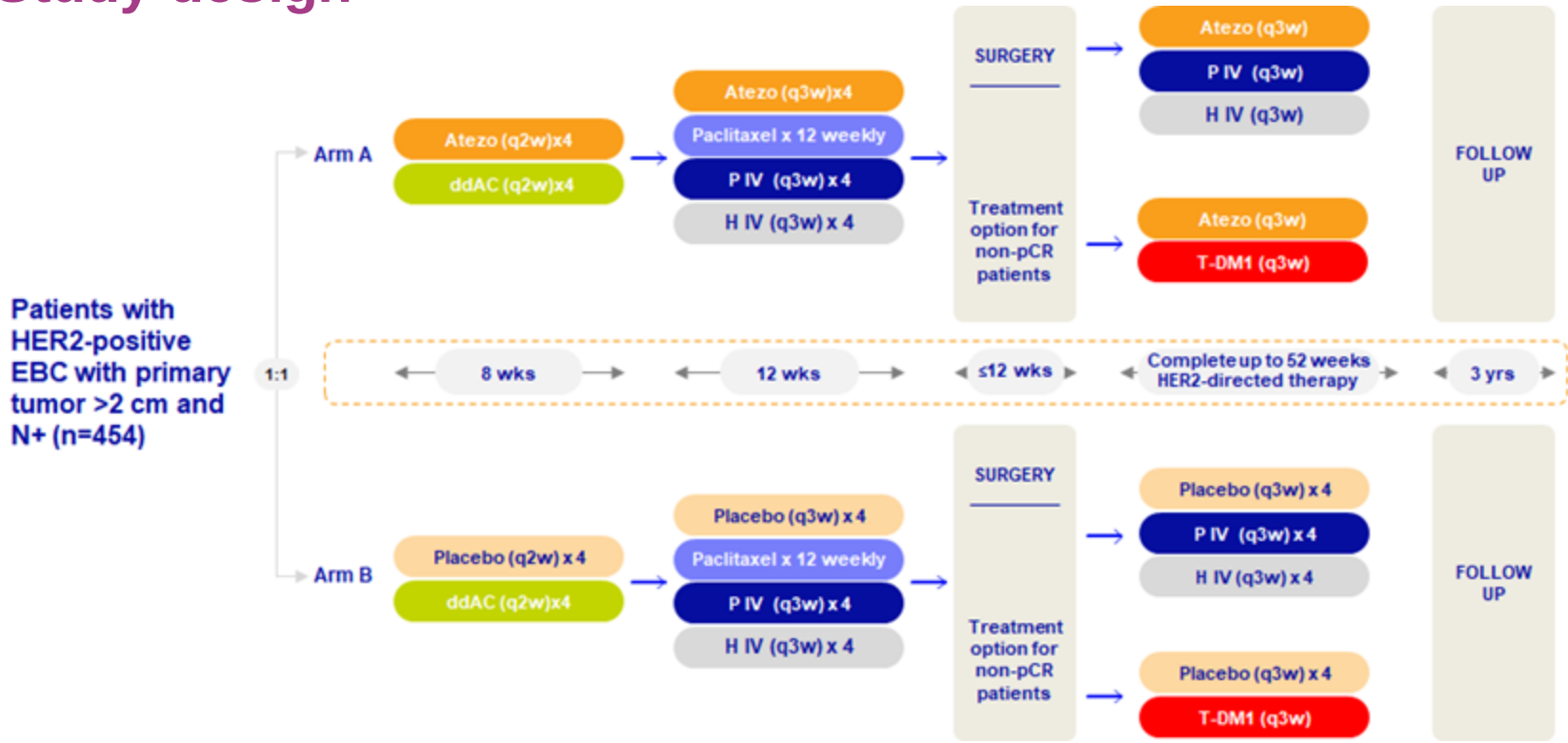


	Atezolizumab + T-DM1	Placebo + T-DM1
Patients with OS event, n (%)	11 (19.3)	8 (29.6)
Median OS (mo)	NE	NE
Stratified HR (95% CI)	0.55 (0.22–1.38)	
1-year survival rate (%)	94.3	87.9

Emens LA, et al. SABCS 2018, ESMO 2019

IMpassion 050:
Atezolizumab in combination with Neoadjuvant - chemotherapy and dual anti HER2 therapy in Early HER2 Positive Breast Cancer

Study design

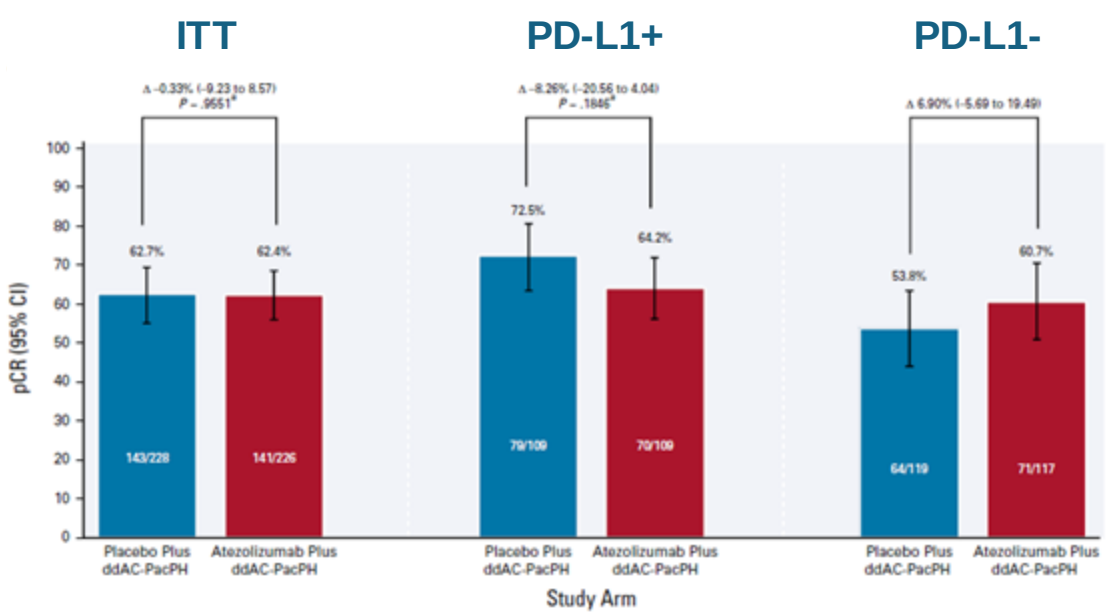


Stratification factors:

- Stage at diagnosis (T2; T3-4)
- HR status (ER+ and/or PgR+; ER- and PgR-) Hormone receptor positive enrollment will be capped at 50%.
- PD-L1 status (IC 0; IC 1/2/3)

IMpassion050 **pCR results** (primary endpoint)

IMpassion050 - early HER2+ eBC



Huober al. (2022)

PD-L1 IHC role for CIT benefit is **unclear**
Suspect tumor heterogeneity plays a role here like in TNBC

Why these results?

1. Really need to stop just ADDING on new IO agents (with overlapping toxicity) to older AC chemo+T/P combinations
2. Diarrhoea, myelosuppression, all prohibitive in allowing Atezo to augment T cell response

In moving fwd IO: patients need trials with
Less chemo, less myelosuppression, less AEs
Less ”add-on” trials
Target high TIL patients (Taxol+Herceptin or T-DXD)
Avoid pertuzumab/ chemo combinations
Go for early stage

APTneo

- The APTneo trial was a randomized neoadjuvant study of the combination of trastuzumab, pertuzumab, carboplatin and paclitaxel (HPCT) with or without atezolizumab in women with early high-risk and locally advanced HER2-positive suitable for neoadjuvant therapy.
- One study arm included anthracycline and cyclophosphamide.

Gianni L, Munzone E, Mansutti M, et al. Pathologic complete response (pCR) of neoadjuvant therapy with or without atezolizumab in HER2-positive, early high-risk and locally advanced breast cancer: APTneo Michelangelo randomized trial. Presented at SABCS 2023. December 5-9, 2023. San Antonio, TX. Abstract LBO1-02.

APTneo

- The open-label phase III APTneo trial enrolled 661 patients with operable or locally advanced HER2-positive breast cancer who had not previously been exposed to chemotherapy.

- **Arm A)** (n=223) received neoadjuvant Q3 week trastuzumab / pertuzumab / carboplatin AUC 2 and paclitaxel 90 mg/m on days 1 and 8 every 21 days for 6 cycles. Adjuvant HP for another 12 cycles.
- **Arm B1)** (n=218) received neoadjuvant doxorubicin /cyclophosphamide Q3 weeks for 3 cycles followed by HPCT for 3 cycles plus atezolizumab at 1200 mg every 3 weeks. Adjuvant HP and atezolizumab for an additional 12 cycles.
- **Arm B2)** (n=220) were given HPCT plus atezolizumab for 6 cycles followed by surgery and adjuvant HP and atezolizumab for an additional 12 cycles.

Gianni L, Munzone E, Mansutti M, et al. Presented at SABCS 2023. December 5-9, 2023. San Antonio, TX. Abstract LBO1-02.

pCR results

- pCR achieved with Atezolizumab plus HPCT with or without anthracyclines vs those given HPCT alone, 57.8% vs 52.0%, respectively (P = .526).
- The pCR achieved with AC and atezolizumab followed by HPCT was significantly higher vs HPCT alone, 61.9% vs 52% (p=.022)
- No significant difference in pCR between who received atezolizumab + HPCT without anthracyclines vs HPCT alone.(p=.091)
- In a multivariate analysis, treatment with anthracyclines, PD-L1-positivity, estrogen receptor negativity, and the presence of ≥30% stromal tumor-infiltrating lymphocytes were associated with a higher probability of pCR.

In the intention-to-treat population, the pCR defined as the absence of invasive cells in the breast and lymph nodes achieved:

	pCR
Arm A HPCT (n=223)	52%
Arm B1 atezo + AC followed by HPCT (n=218)	61.9%
Arm B2 atezo + HPCT (n=220)	53.6%

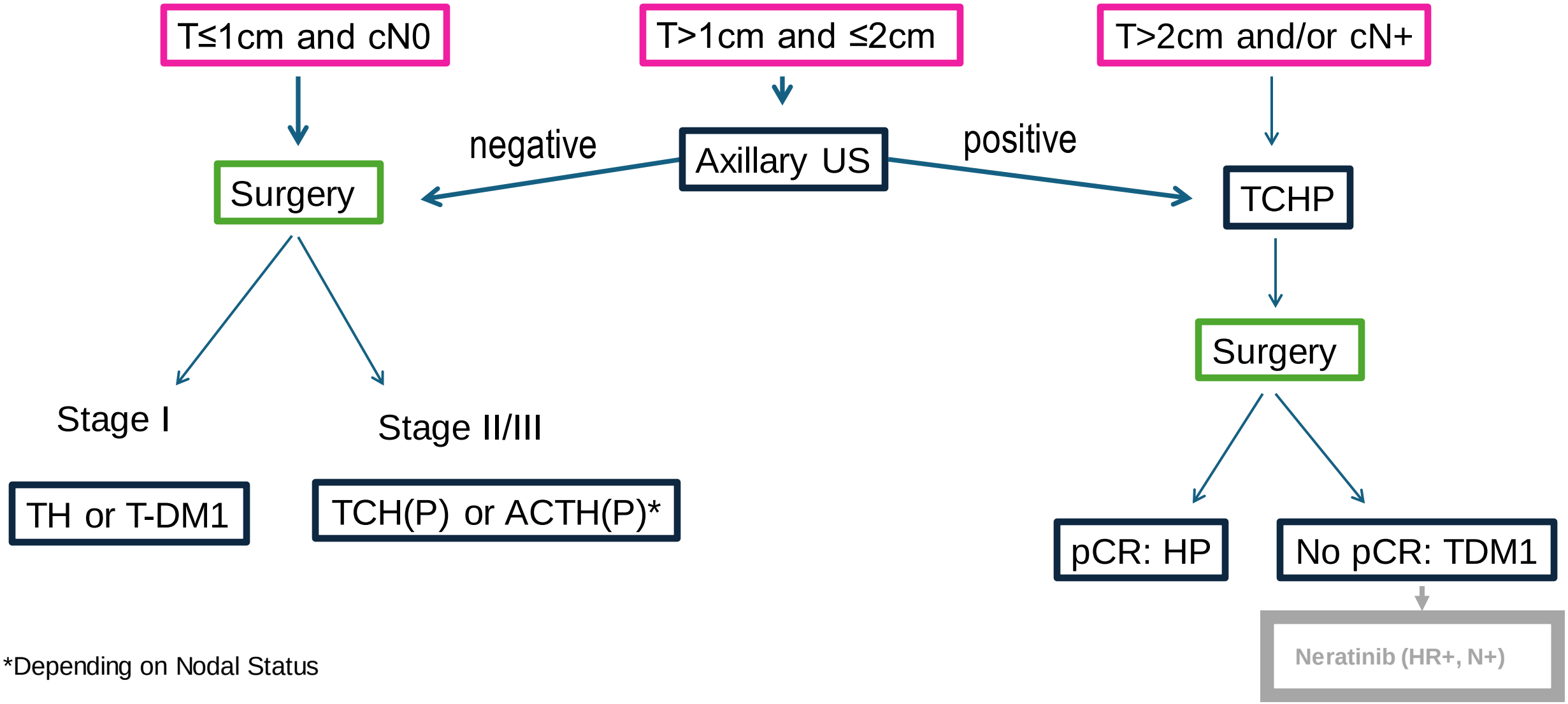
P=.022

P=0.91

P=0.89

Gianni L, Munzone E, Mansutti M, et al. Presented at SABCS 2023. December 5-9, 2023. San Antonio, TX. Abstract LBO1-02.

HER2+ Early Breast Cancer Algorithm



*Depending on Nodal Status