Novità nel trattamento della malattia HER2-positiva

Antonella Ferro

Trento

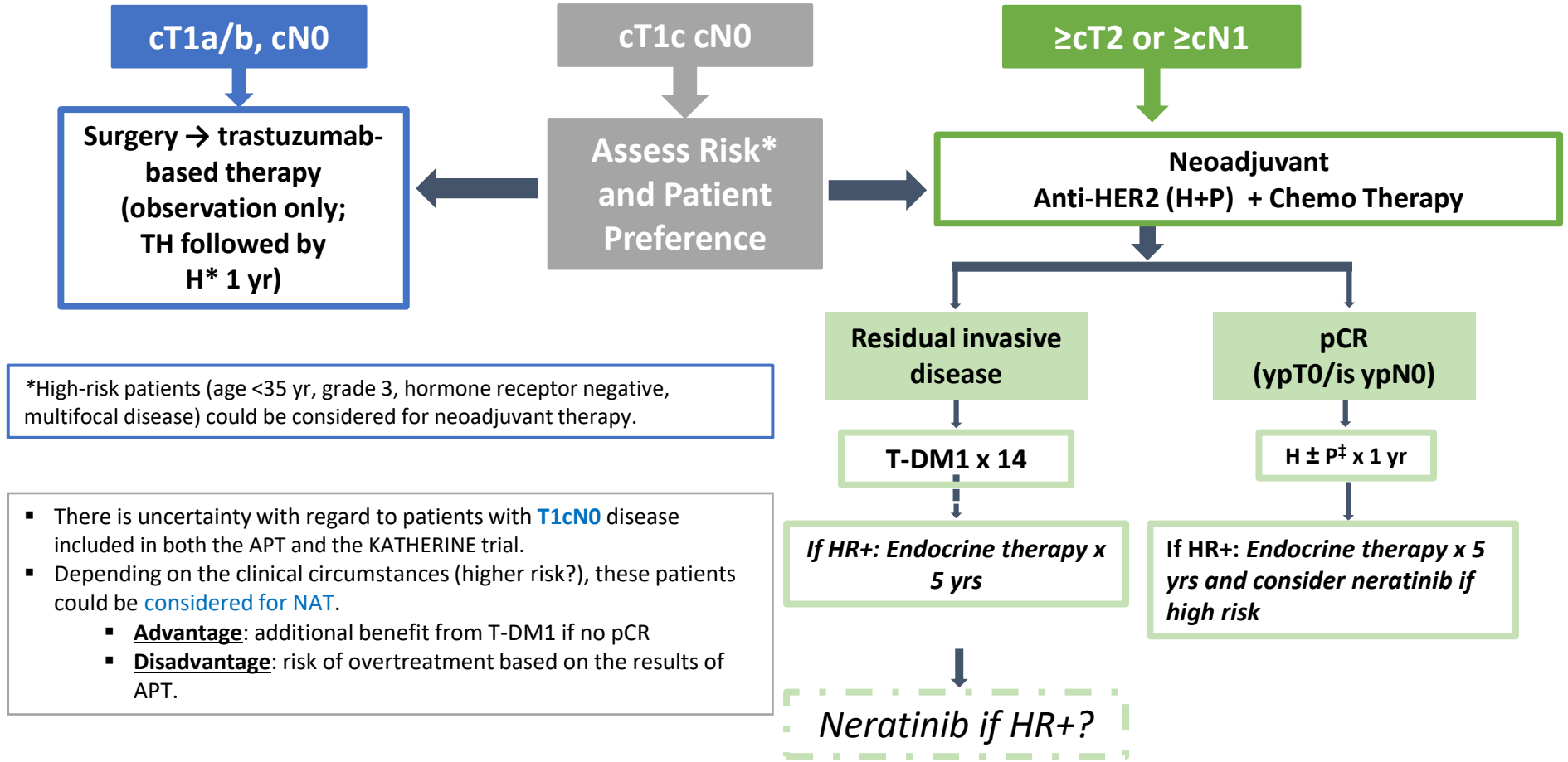
Disclosure

- Honoraria: Pfizer, Novartis, Daiichi Sankyo, Ely Lilly, Seagen, Gilead, Astra Zeneca
- Travel support: Ipsen, Novartis
- Research support (to the Institution): Pfizer

The era of personalized medicine in HER2+ EBC

- The favorable outcomes of HER2+ breast cancers provide opportunity to:
  - De-escalate therapy for lower risk patients to reduce the toxicities of treatment
  - Escalate therapy for minority of patients who are risk for recurrence despite maximal current management

Strategy for Managing Patients With Stage I-III HER2+ EBC



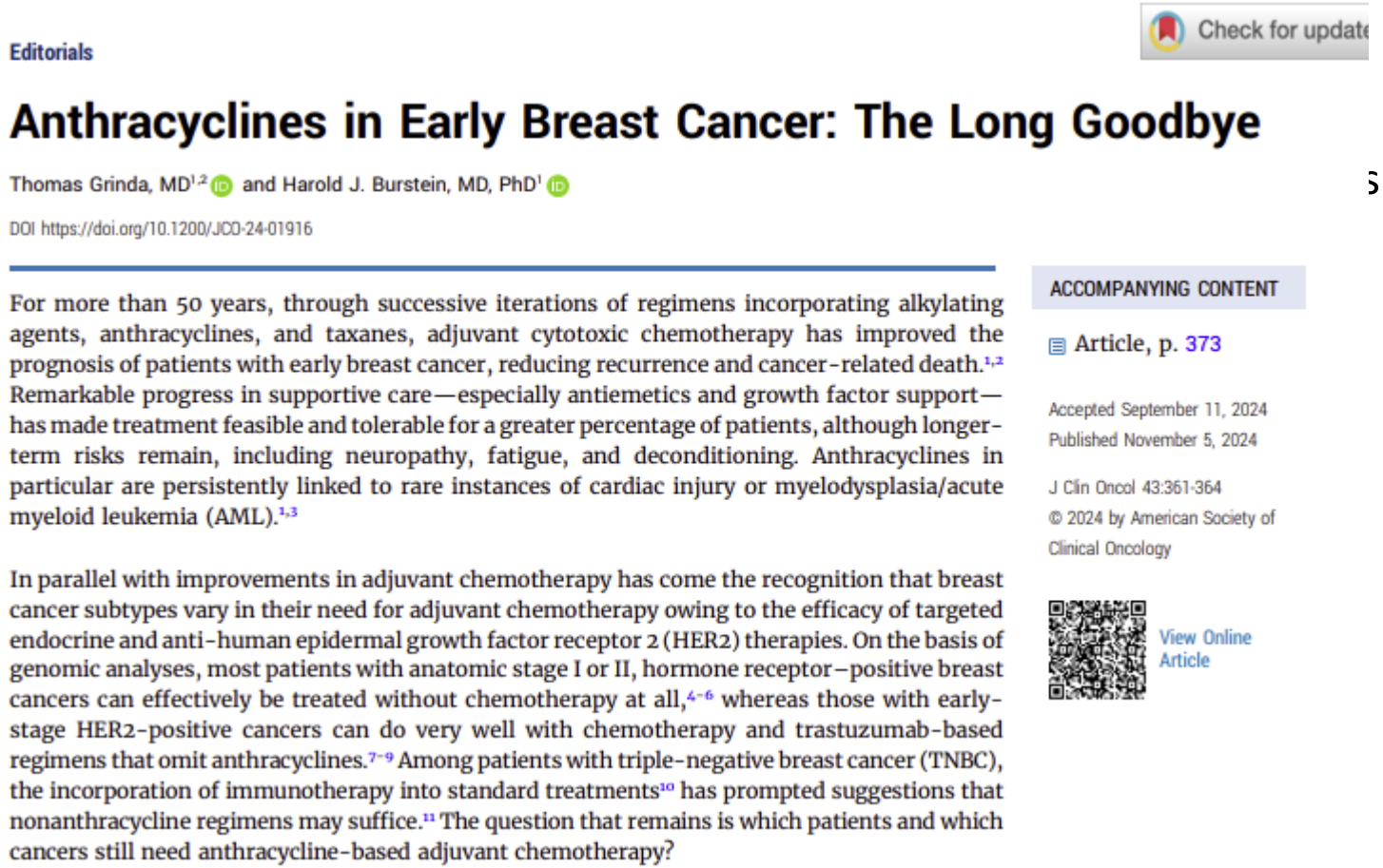
*High-risk patients (age <35 yr, grade 3, hormone receptor negative, multifocal disease) could be considered for neoadjuvant therapy.

- There is uncertainty with regard to patients with **T1cN0** disease included in both the APT and the KATHERINE trial.
- Depending on the clinical circumstances (higher risk?), these patients could be considered for NAT.
  - **Advantage**: additional benefit from T-DM1 if no pCR
  - **Disadvantage**: risk of overtreatment based on the results of APT.

Barcenas. Ann Oncol. 2020; 31:1223. ESMO Guidelines 2024

DE-ESCALATION STRATEGIES

- Short Trastuzumab durations
  - Only Persephone demonstratec
    the optimal duration!
- Avoiding anthracyclines
  - BCIRG 006
  - TRAIN 2
- Small tumors (Remove part of t
  - APT: paclitaxel + trastuzumab
  - ATTEMPT: T-DM1



Editorials

Anthracyclines in Early Breast Cancer: The Long Goodbye

Thomas Grinda, MD[1,2] and Harold J. Burstein, MD, PhD[1]

DOI https://doi.org/10.1200/JCO-24-01916

For more than 50 years, through successive iterations of regimens incorporating alkylating agents, anthracyclines, and taxanes, adjuvant cytotoxic chemotherapy has improved the prognosis of patients with early breast cancer, reducing recurrence and cancer-related death.[1,2] Remarkable progress in supportive care—especially antiemetics and growth factor support—has made treatment feasible and tolerable for a greater percentage of patients, although longer-term risks remain, including neuropathy, fatigue, and deconditioning. Anthracyclines in particular are persistently linked to rare instances of cardiac injury or myelodysplasia/acute myeloid leukemia (AML).[1-3]

In parallel with improvements in adjuvant chemotherapy has come the recognition that breast cancer subtypes vary in their need for adjuvant chemotherapy owing to the efficacy of targeted endocrine and anti-human epidermal growth factor receptor 2 (HER2) therapies. On the basis of genomic analyses, most patients with anatomic stage I or II, hormone receptor–positive breast cancers can effectively be treated without chemotherapy at all,[4-6] whereas those with early-stage HER2-positive cancers can do very well with chemotherapy and trastuzumab-based regimens that omit anthracyclines.[7-9] Among patients with triple-negative breast cancer (TNBC), the incorporation of immunotherapy into standard treatments[10] has prompted suggestions that nonanthracycline regimens may suffice.[11] The question that remains is which patients and which cancers still need anthracycline-based adjuvant chemotherapy?

ACCOMPANYING CONTENT

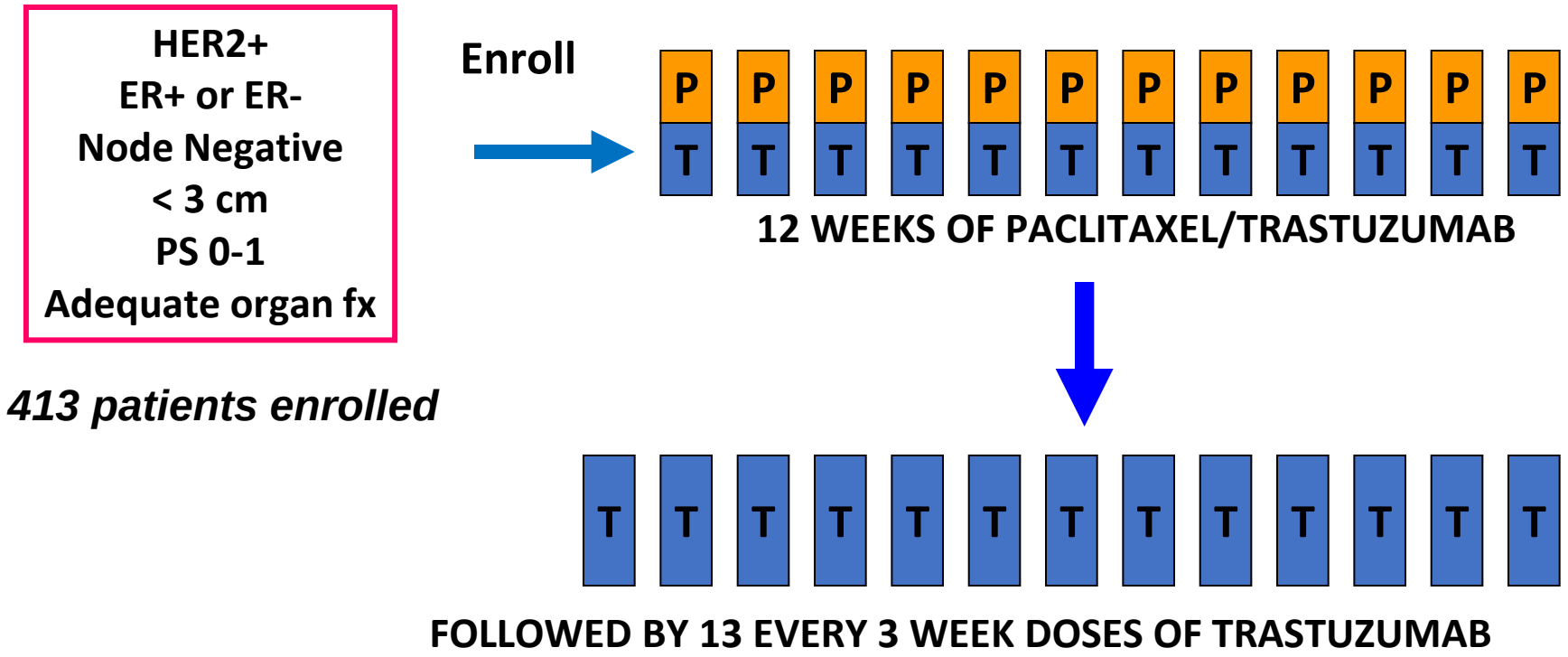
Article, p. 373

Accepted September 11, 2024
Published November 5, 2024

J Clin Oncol 43:361-364

View Online Article

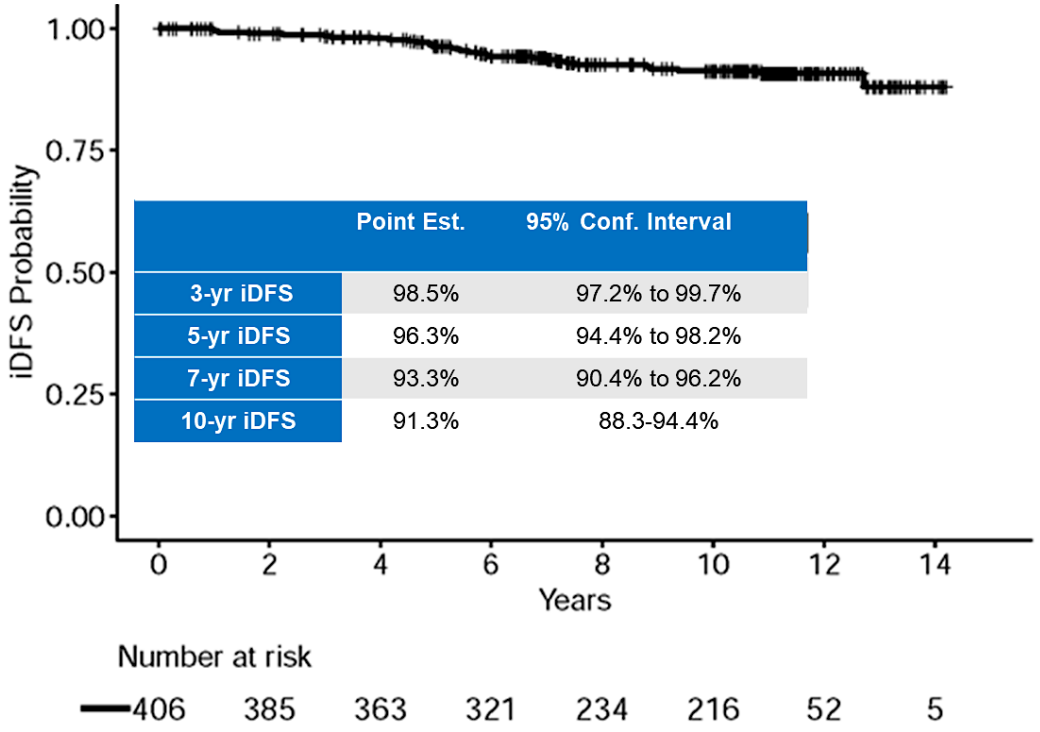
APT: Can we leverage the effectiveness of trastuzumab to de-escalate chemotherapy in low-risk HER2+ breast cancer?



Trial designed to determine if treatment with paclitaxel/trastuzumab is associated with a low (5%) rate of recurrence after 3 years

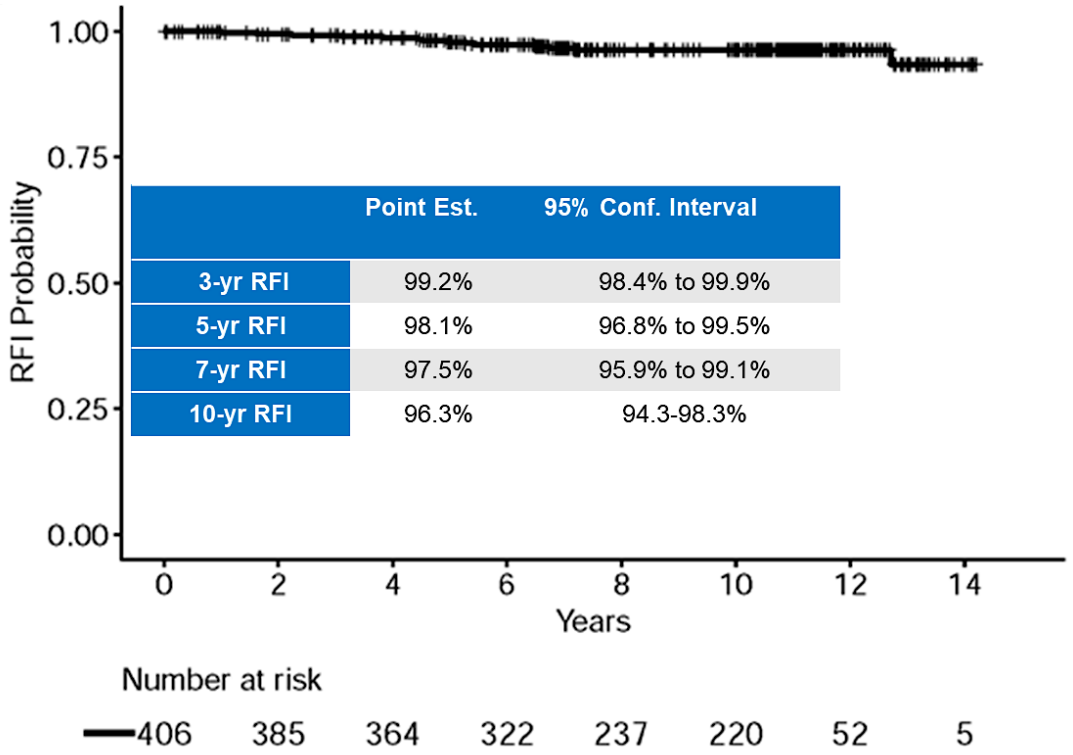
APT: OUTCOMES AT 10 YRS

DISEASE-FREE SURVIVAL



	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%

RECURRENCE FREE INTERVAL



	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%

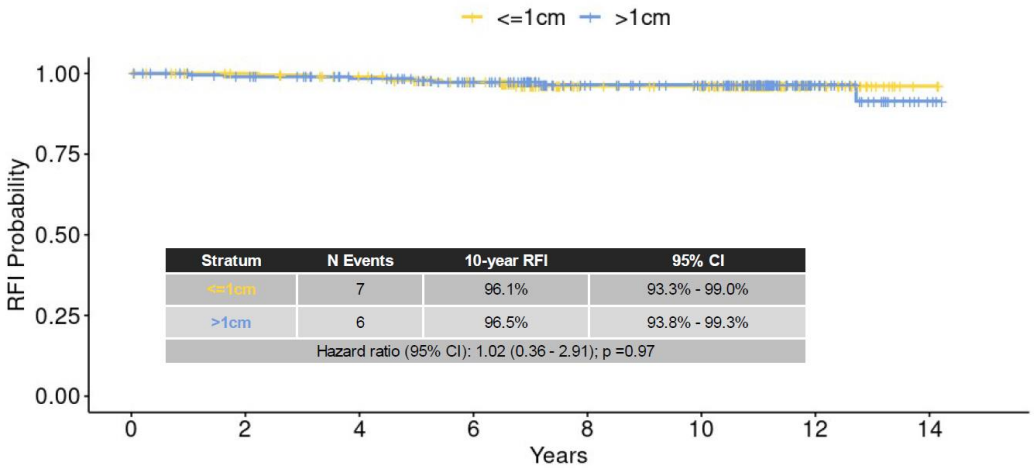
6 (1.5%) distant recurrence events

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

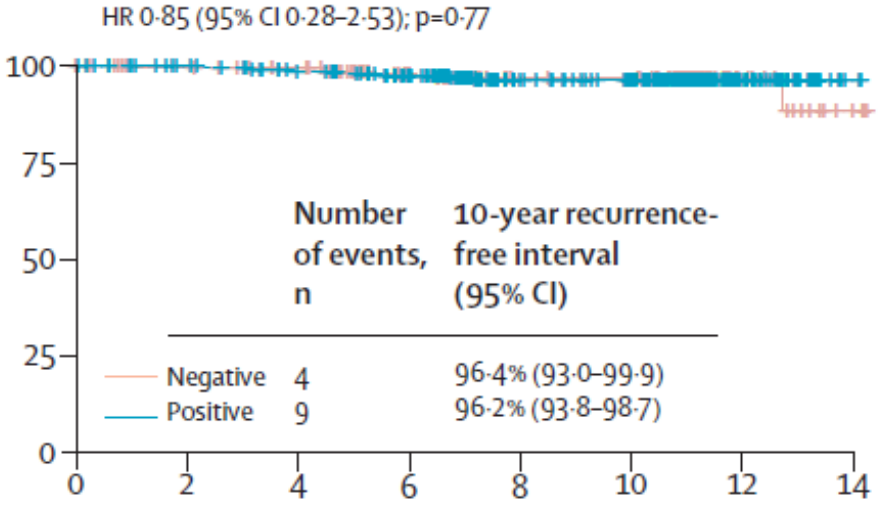
Tolaney SM et al, Lancet Onc 2023

APT: OUTCOMES AT 10 YRS

By Tumor Size



By Hormone receptor Status



The trial cannot tell us which patients do not need any systemic therapy

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

Tolaney SM et al, Lancet Onc 2023

Replace cytotoxic therapy with a targeted drug

ATTEMPT Trial

- A randomized (3:1), open-label phase II study

Stratified by age (<55, ≥ 55), planned radiation therapy (Y/N), planned hormonal therapy (Y/N)

Women with stage 1 HER2+ BC with N0 or N1mic disease; LVEF ≥ 50%; no prior invasive BC surgery; ≤ 90 days from last surgery (N = 497)

- **T-DM1** 3.6 mg/kg IV Q3W x 17 (n = 383)
- **Paclitaxel** 80 mg/m2 IV + **Trastuzumab** 2 mg/kg IV Q1W x 12 (n = 114)
- **Trastuzumab** 6 mg/kg Q3W x 13

Follow-up for 5 yrs after final dose of T-DM1 or TH

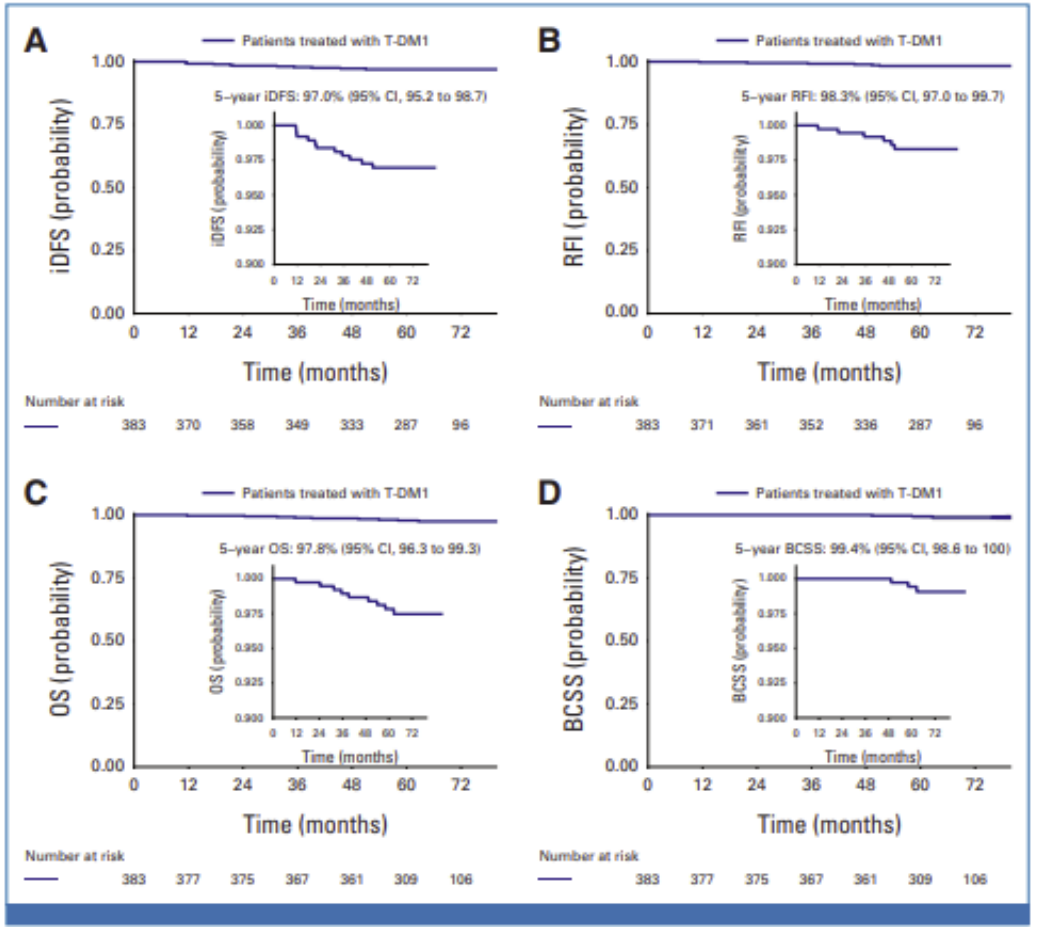
Study not powered to assess efficacy of TH or to compare efficacy of T-DM1 to TH

- Coprimary endpoints: 3-yr DFS in T-DM1; comparison of incidence of clinically relevant toxicities with T-DM1 vs TH, including: grade ≥ 3 non-hematologic AEs, grade ≥ 2 neurotoxicity, grade ≥ 4 hematologic AEs, febrile neutropenia, and any AE requiring dose delay or discontinuation of protocol therapy

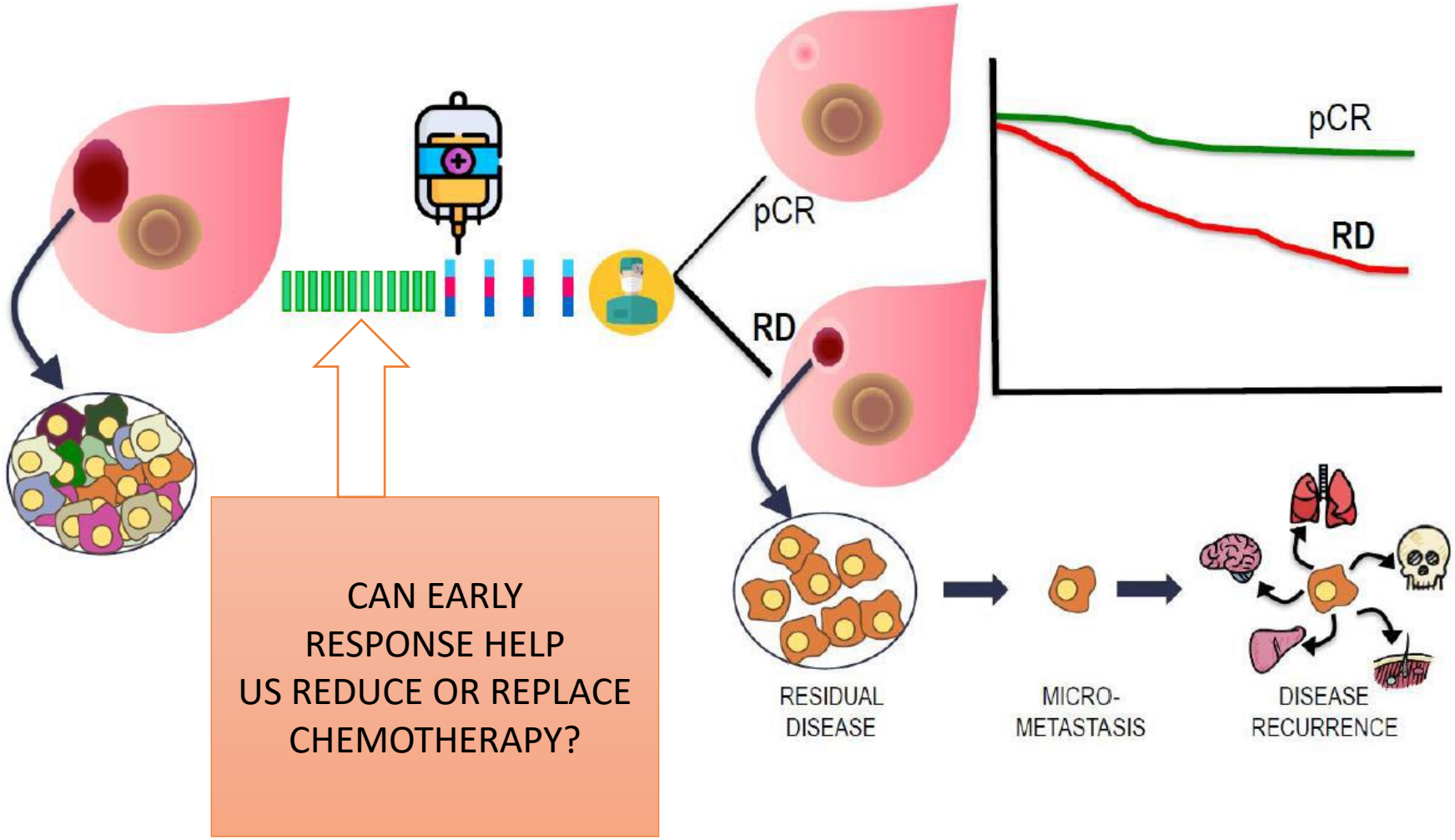
Tolaney S et al JCO 2021
Tolaney S et al Lancet Oncol 2023
Tarantino P et al JCO 2024

ATEMPT: CLINICALLY RELEVANT TOXICITY

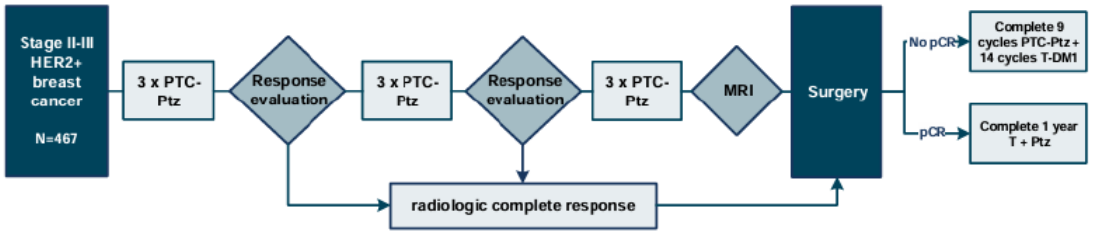
Clinically Relevant Toxicity	T-DM1 (n = 383) N (%)	TH (n = 114) N (%)
Grade ≥3 non-hematologic toxicity	37 (10%)	13 (11%)
Grade ≥ 2 neurotoxicity	42 (11%)	26 (23%)
Grade ≥4 hematologic toxicity	4 (1%)	0 (0%)
Febrile neutropenia	0 (0%)	2 (2%)
Any toxicity requiring dose delay	106 (28%)	30 (26%)
Any toxicity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



Tailored therapy: Image –guided optimization (MRI, PET-CT)



TRAIN III Study (Louis et al, RS1-03, SABCS 2024)

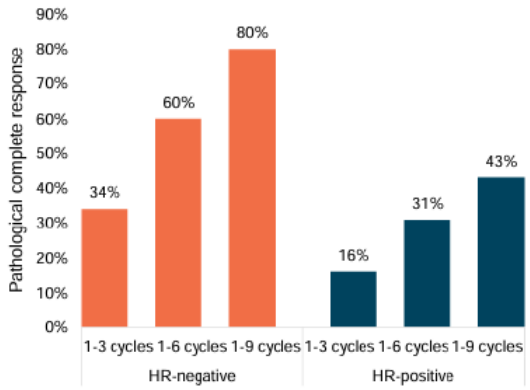


Primary endpoint: 3-yr EFS
Secondary endpoints: AEs, pCR (ypT0/is, N0), rCR, HR-QoL, 3-,5-,10-yr EFS/OS
PTC-Ptz = cycles of 3 weeks: day 1 PTC + Ptz; day 8 only P. P = paclitaxel 80 mg/m² i.v.; C = carboplatin AUC 6 mg•ml/min i.v.;
T = trastuzumab 6 mg/kg i.v.; Ptz = pertuzumab 420 mg i.v.

Radiological complete response (rCR): complete remission on MRI breast & axillary ultrasound combined with negative FNA/core biopsy in baseline N+ & negative vacuum assisted core biopsies of the marked original tumor region in HR+ patients

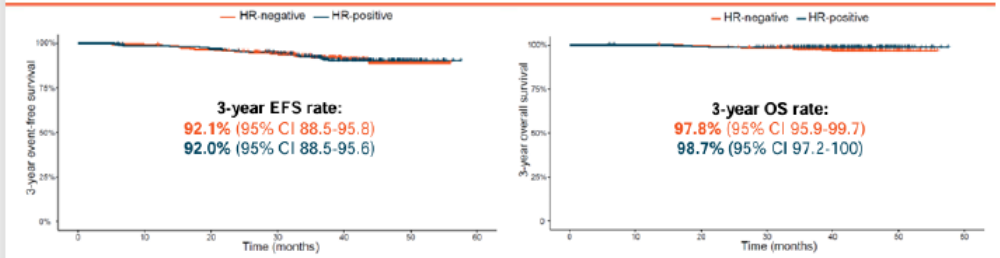
The regimen would be considered successful if no more than 38 events occurred in the HR- group, and no more than 34 events occurred in the HR+ group after 700 patient-years of follow-up.

	HR-negative (N=235)	HR-positive (N=232)
Age (median)	52	50
Clinical tumor stage		
cTx-cT0-cT1	25 (11%)	24 (10%)
cT2-T3	205 (87%)	200 (86%)
cT4	5 (2%)	8 (3%)
Nodal status		
Negative	93 (40%)	94 (41%)
Positive	142 (60%)	137 (59%)
HER2-status		
2+ and ISH+	14 (6%)	43 (19%)
3+	207 (88%)	178 (77%)
Unknown and ISH+	14 (6%)	11 (5%)



MRI accuracy (NPV) to predict a pCR:
HR-negative = 87%, HR-positive 53%

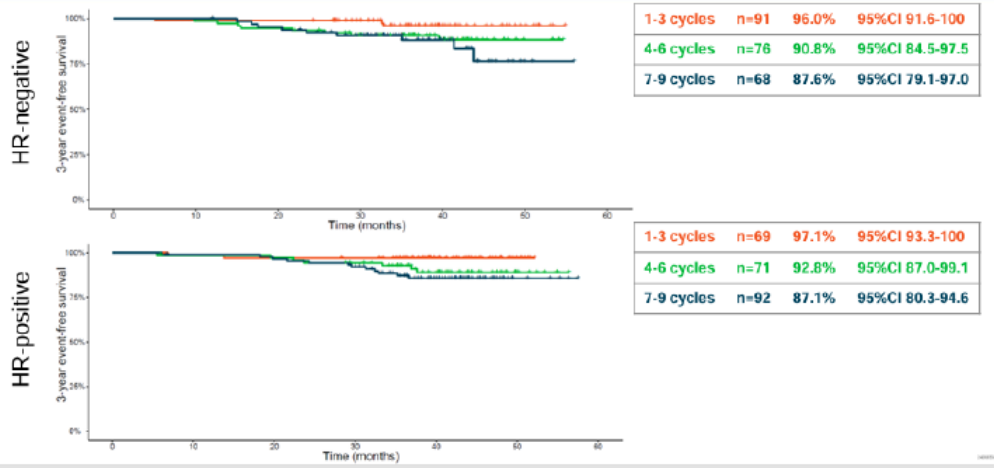
3-year event-free and overall survival



	HR-negative (N=236)	HR-positive (N=232)
Event-free survival events	19	21
Distant recurrence	9	8
Brain metastases	6	3
Locoregional recurrence	7	6
Second primary non-breast cancer	2	4
Second primary breast cancer	0	3
Death	1	0

Primary endpoint was met with <38 events in HR- patients (p=0.001) and <34 events in HR+ patients (p=0.023)

3-year EFS by number of neoadjuvant cycles



One in three patients with HR-/HER2+ and one in six with HR+/HER2+ breast cancer achieve a pCR with only three cycles of neoadjuvant chemotherapy

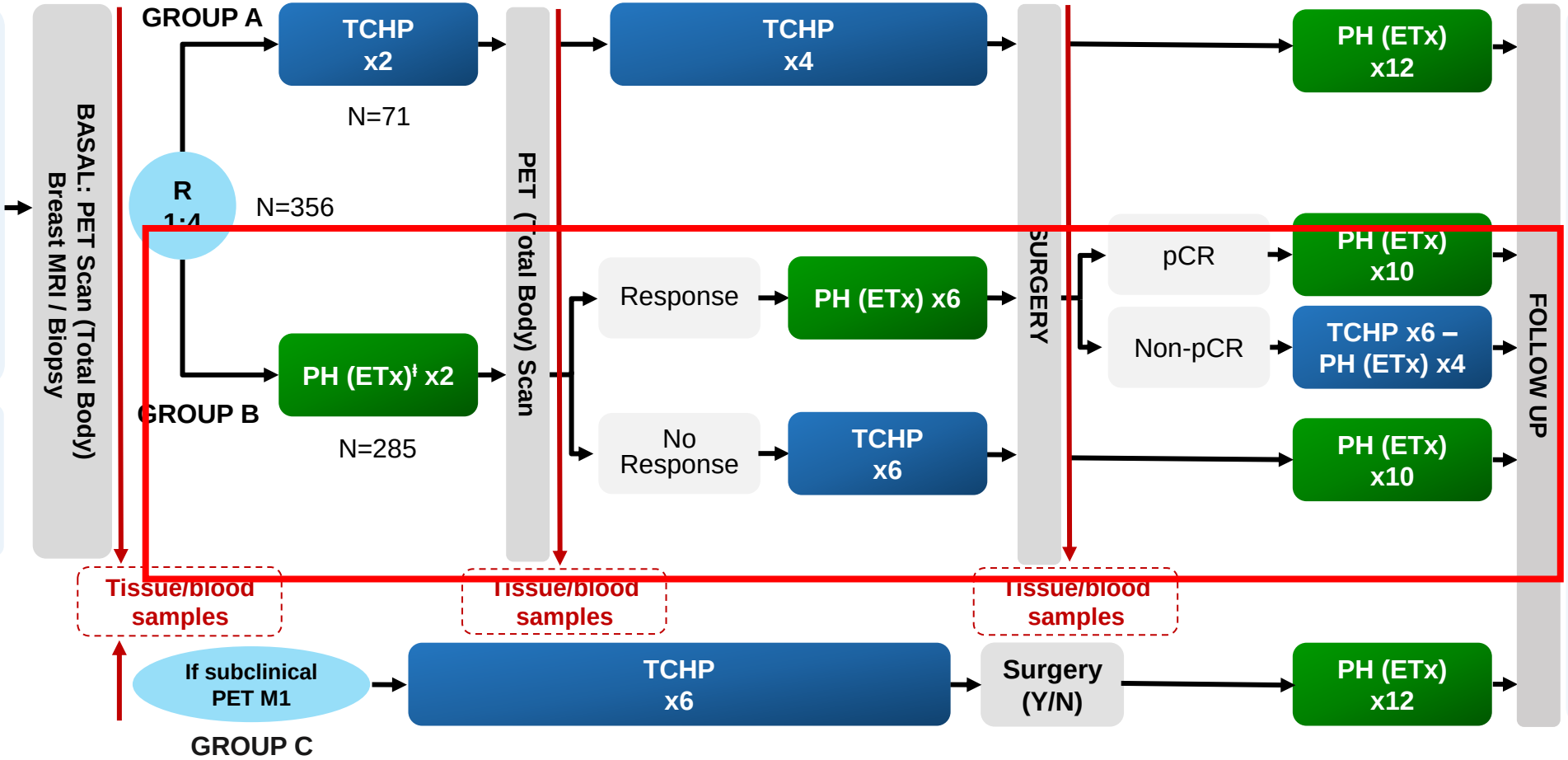
PHERGain: Can PET response be used to guide therapy de-escalation in HER2+ EBC?

Key Eligibility Criteria

1. Centrally confirmed HER2[+] stage I-IIIA EBC.
2. Tumor diameter ≥ 1.5 cm by MRI or ultrasound.
3. Presence of a breast PET-evaluable lesion.

Stratification factors

- Hormonal receptor status (+/-)



First Primary Endpoint

- pCR in PET Responders (Arm B)

Second Primary Endpoint

- 3-year iDFS rate in Arm B

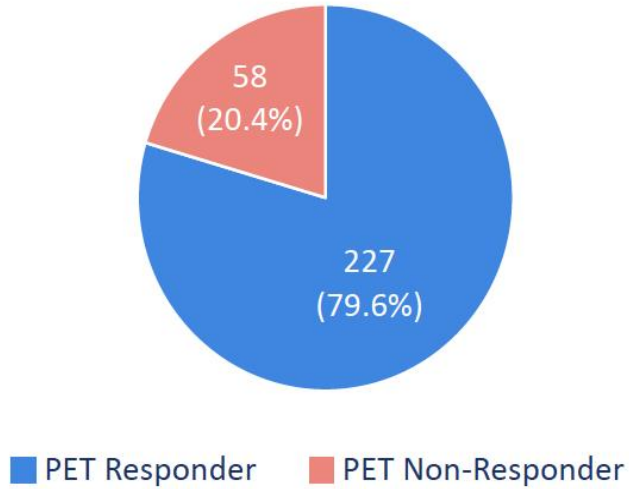
C: Carboplatin; D: Docetaxel; EBC: Early breast cancer; ETx: Endocrine therapy (letrozole post-menopausal/tamoxifen pre-menopausal), Adjuvant ETx up to 3 years from surgery; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; H: Trastuzumab SC; HER2: Human Epidermal Growth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

phergain

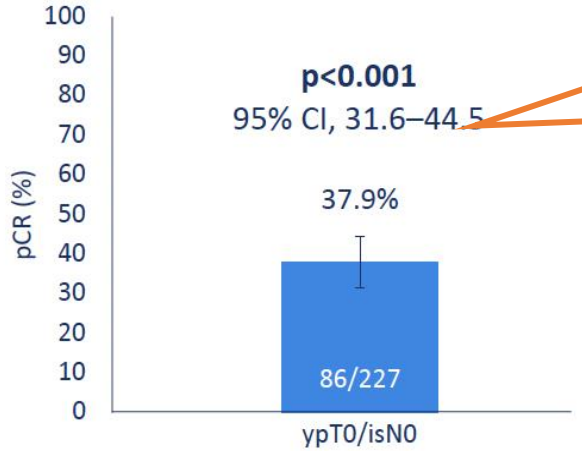
Primary Endpoint: pCR in ^{18}F-FDG-PET responders in group B

PET Responders and Non-Responders



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

pCR rate

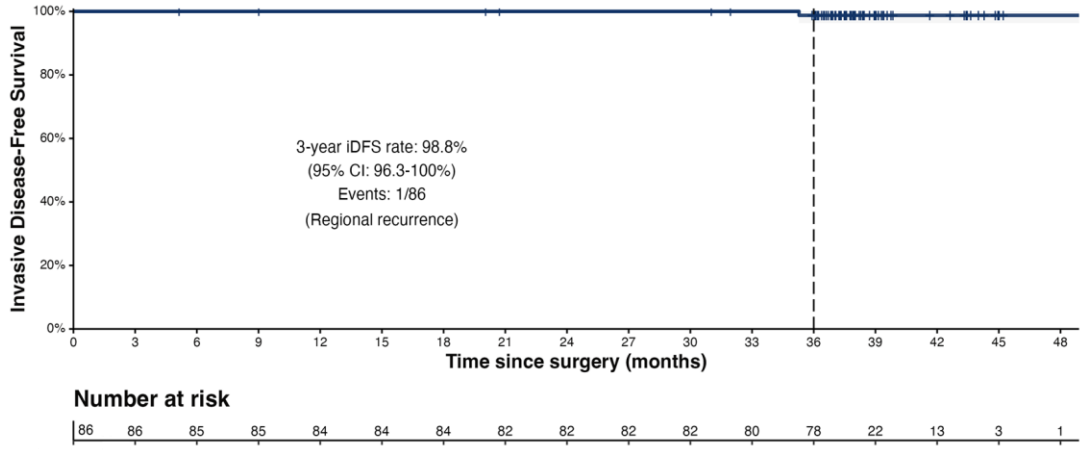


Challenge: 40% achieved pCR with HP… but

…60% need escalated adjuvant therapy!!!

Null hypothesis: pCR ≤20%

Subgroup analysis: 3-y iDFS rate without CT in PET responders with pCR (n=86)



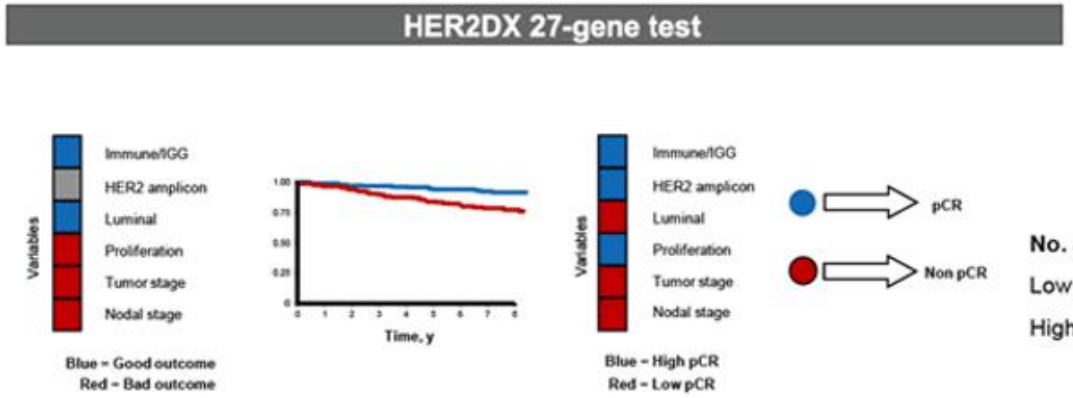
Can we use upfront biomarker selection?

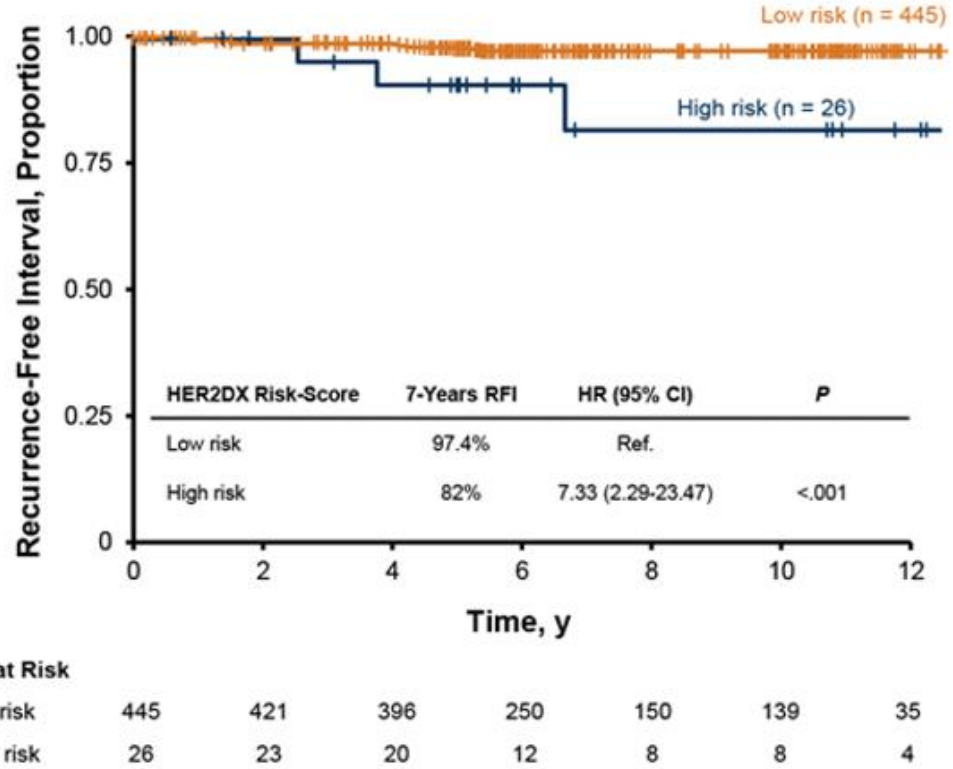
HER2DX

Tils

HER2DX

- **HER2DX** is a tool incorporating tumor size, nodal staging, and 4 gene expression signatures tracking **immune infiltration**, **tumor cell proliferation**, **luminal differentiation**, and the **expression of the HER2 amplicon**, into a single score.
- In a combined analysis of APT and ATEMPT, the HER2DX risk score was found able to identify a population of patients with higher risk of recurrence





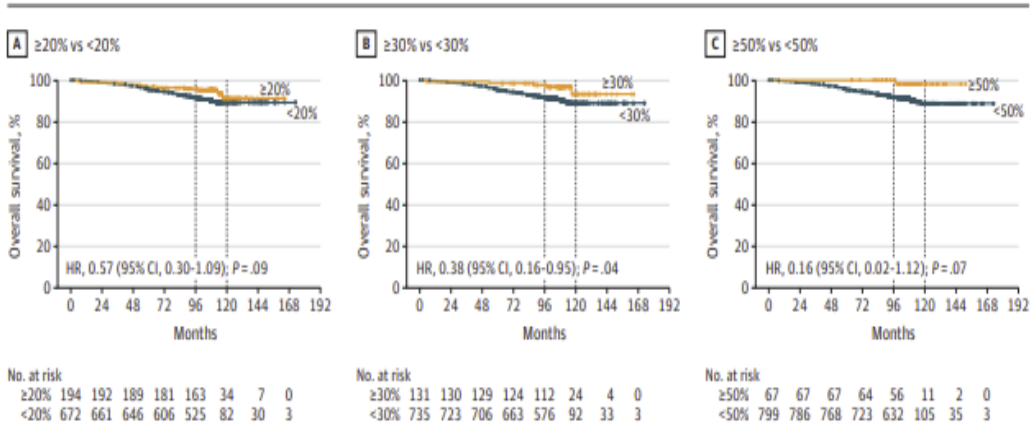
1. Prat A et al. *EBioMedicine*. 2022;75:103801. 2. Tarantino P et al. ESMO Breast 2023. Abstract 6P.

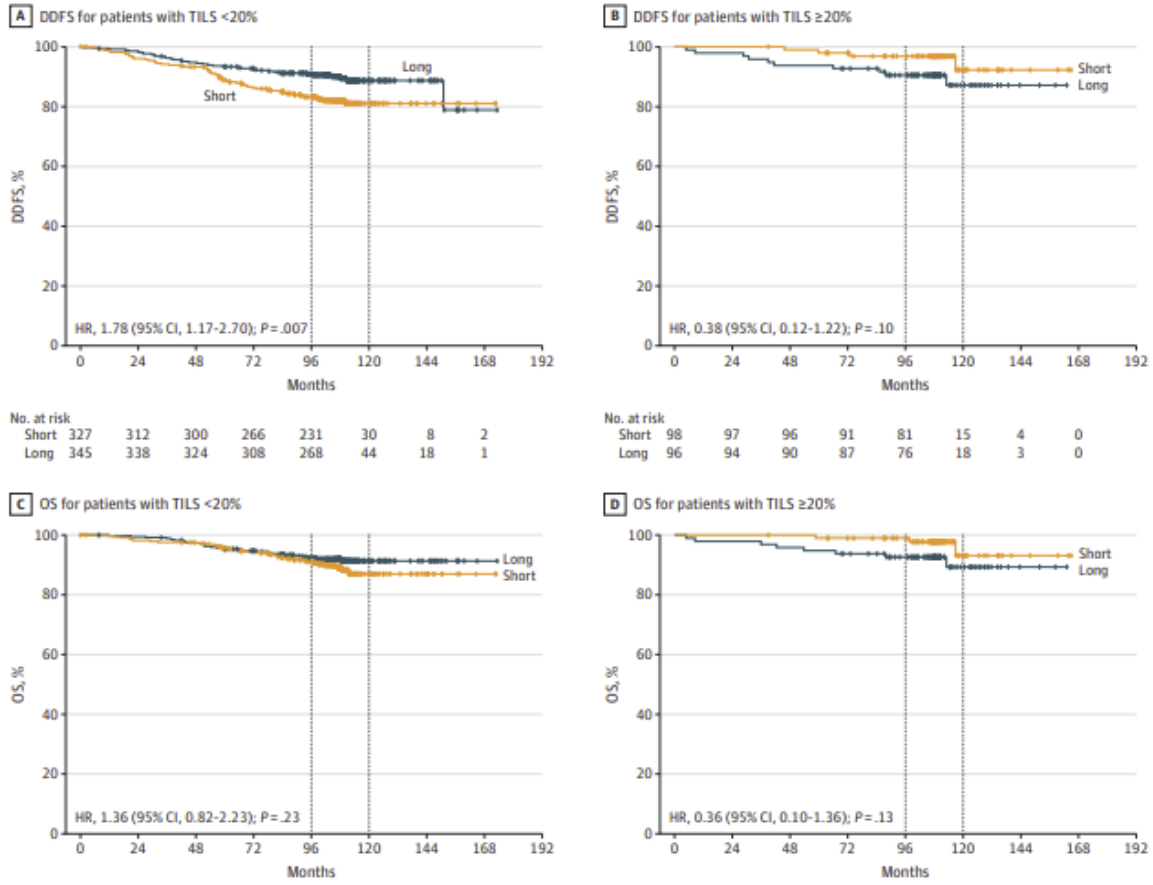
JAMA Oncology | Original Investigation

Tumor-Infiltrating Lymphocytes and Survival Outcomes in Early *ERBB2*-Positive Breast Cancer

10-Year Analysis of the ShortHER Randomized Clinical Trial

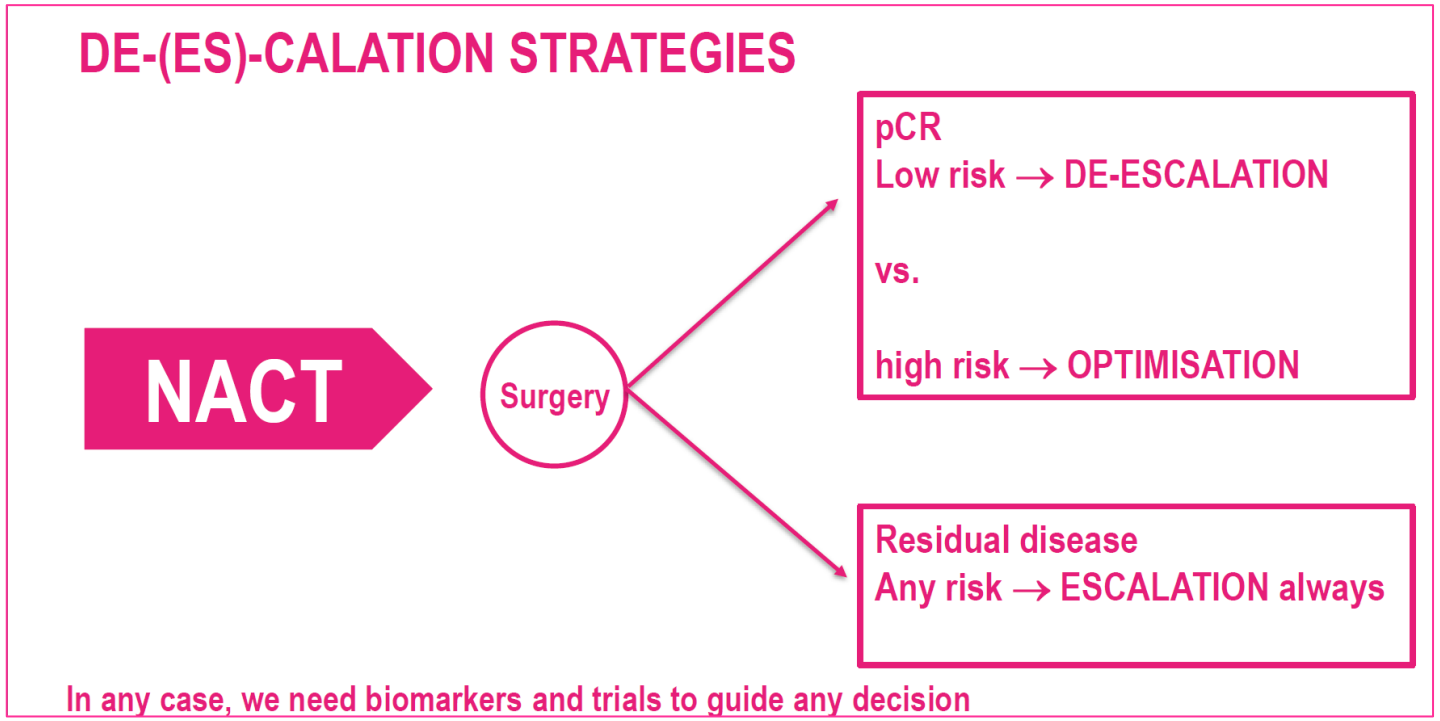
Maria Vittoria Dieci, MD; Giancarlo Bisagni, MD; Stefania Bartolini, MD; Alessio Schirone, MD; Luigi Cavanna, MD; Antonino Musolino, PhD; Francesco Giotta, MD; Anita Rimanti, MD; Ornella Garrone, MD; Elena Bertone, MD; Katia Cagossi, MD; Samanta Sarti, MD; Antonella Ferro, MD; Federico Piacentini, PhD; Enrico Orvieto, MD; Melinda Sanders, MD; Federica Miglietta, PhD; Davide Massa, MD; Sara Balduzzi, PhD; Pierfranco Conte, MD; Roberto D'Amico, PhD; Valentina Guarneri, PhD





Patients with TILs 20% or higher who de-escalated trastuzumab duration and chemotherapy dose were not exposed to an excess risk of distant relapse or death

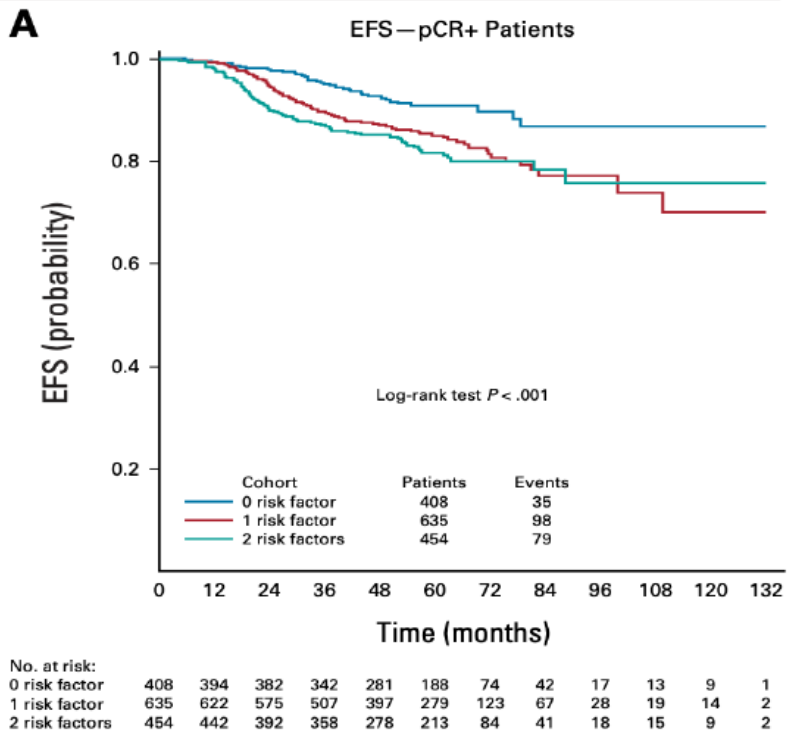
- Patient selection is crucial in either escalating or de-escalating strategies
  - High risk population require more treatments, even after pCR
- Urgent need for biomarkers to identify those patients requiring “more” or “less”treatment
- HER2-positive breast cancer is not a uniform entity
- Clinical trials to escalate or de-escalate systemic therapy in HER2-positive disease should increasingly consider, beyond pCR/RD, the hormone receptor status and the intrinsic molecular subtypes

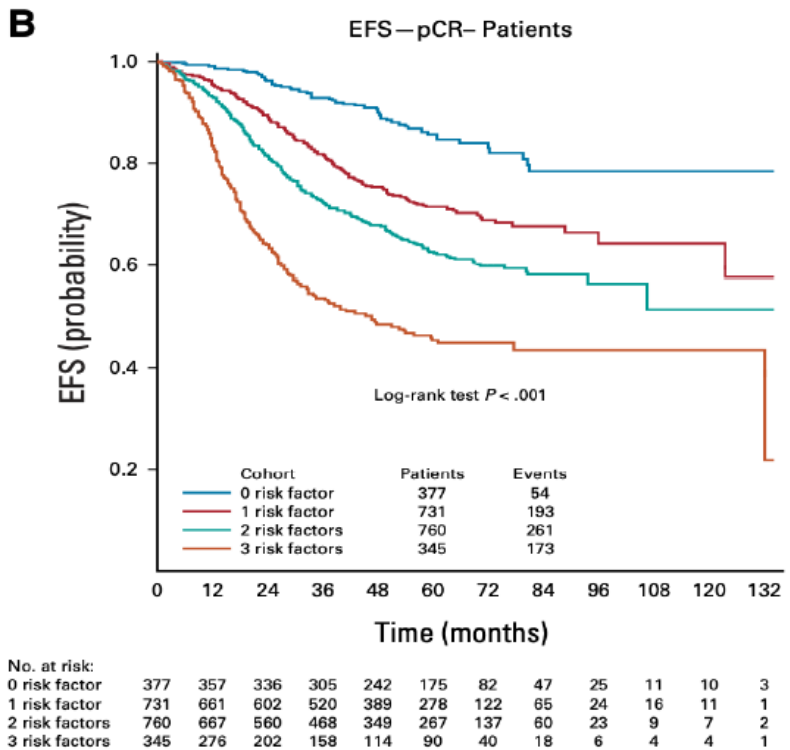


Pathologic Complete Response and Individual Patient Prognosis after NACT plus anti-HER2 therapy in HER2+ early BC

TABLE 2. Multivariate Cox Models for EFS and OS According to pCR

	pCR−				pCR+			
	EFS		OS		EFS		OS	
Prognostic Factor	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
cT (cT1-2 *v* cT3-4)	0.62 (0.53 to 0.73)	<.001	0.47 (0.37 to 0.60)	<.001	0.67 (0.50 to 0.90)	.007	0.55 (0.34 to 0.87)	.011
cN (cN− *v* cN+)	0.66 (0.55 to 0.79)	<.001	0.75 (0.58 to 0.96)	.025	0.72 (0.53 to 0.98)	.039	0.61 (0.36 to 1.03)	.065
Hormone receptor status (hormone receptor+ *v* hormone receptor−)	0.59 (0.50 to 0.68)	.005	0.44 (0.36 to 0.55)	<.001	0.97 (0.73 to 1.29)	.842	0.76 (0.47 to 1.22)	.251

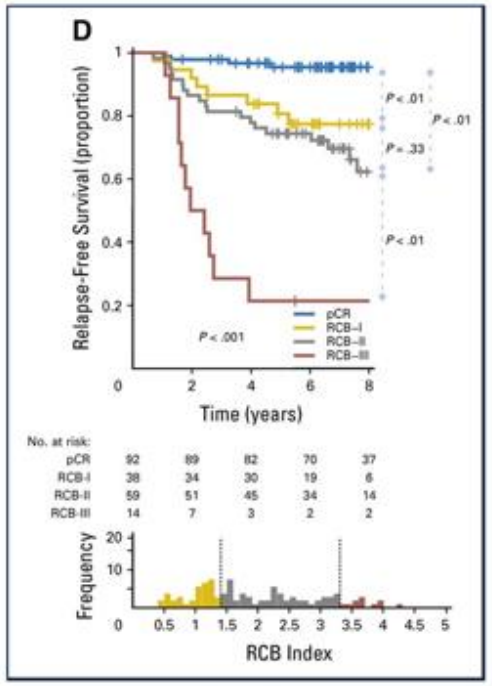




van Mackelenbergh MT,
J Clin Oncol. 2023 41:2998-3008

Need for Approach to Patients with RD (high risk) using preoperative therapy to adapt adjuvant treatment

Outcomes for HER2+ BC treated with trastuzumab-based therapy



Symmans et al. JCO 2017

Post-neoadjuvant approach

Katherine update results

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

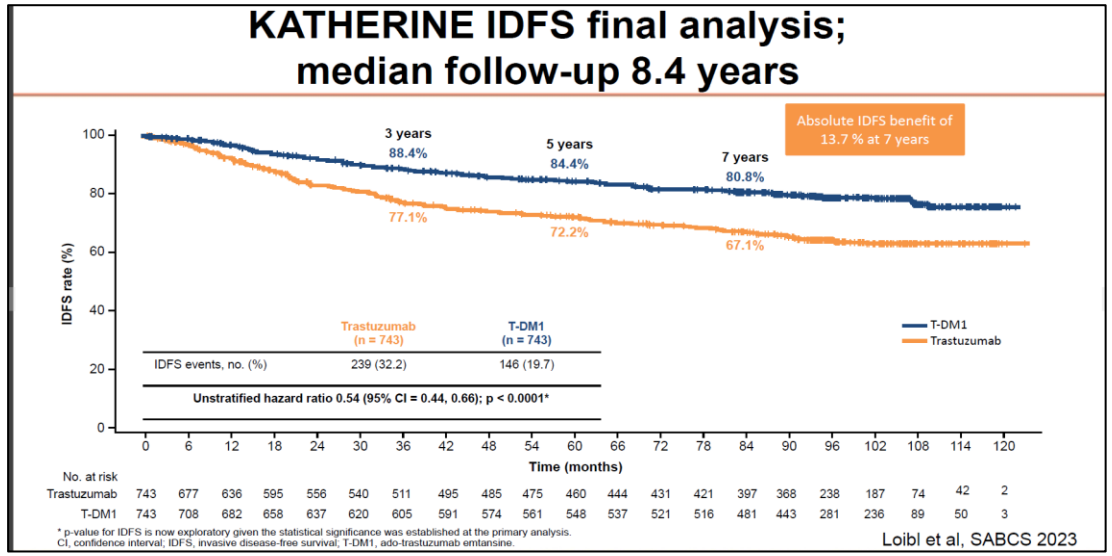
This content is available to subscribers. Subscribe now. Already have an account?

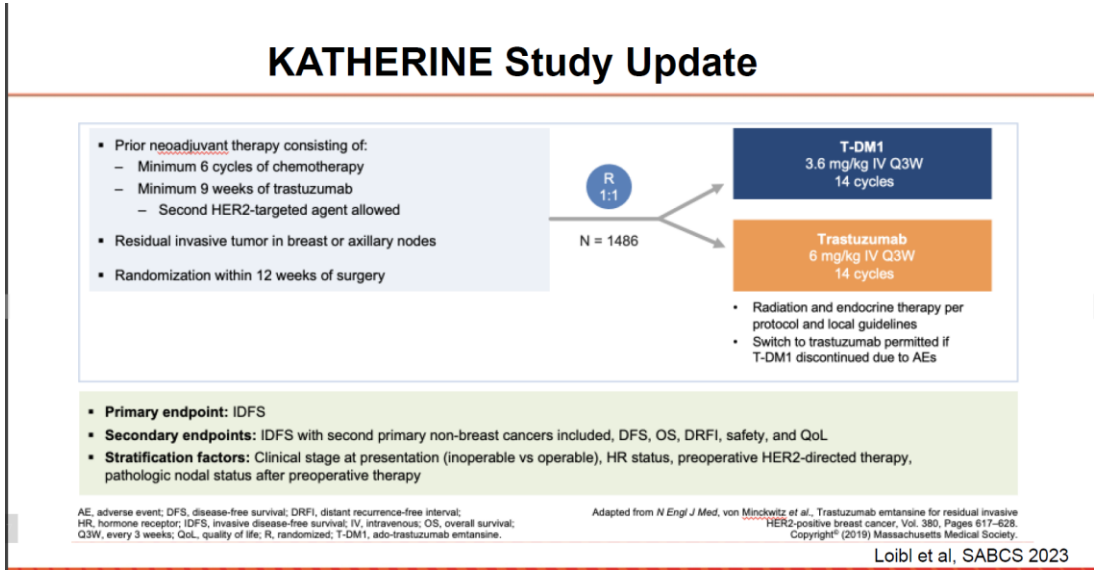
ORIGINAL ARTICLE

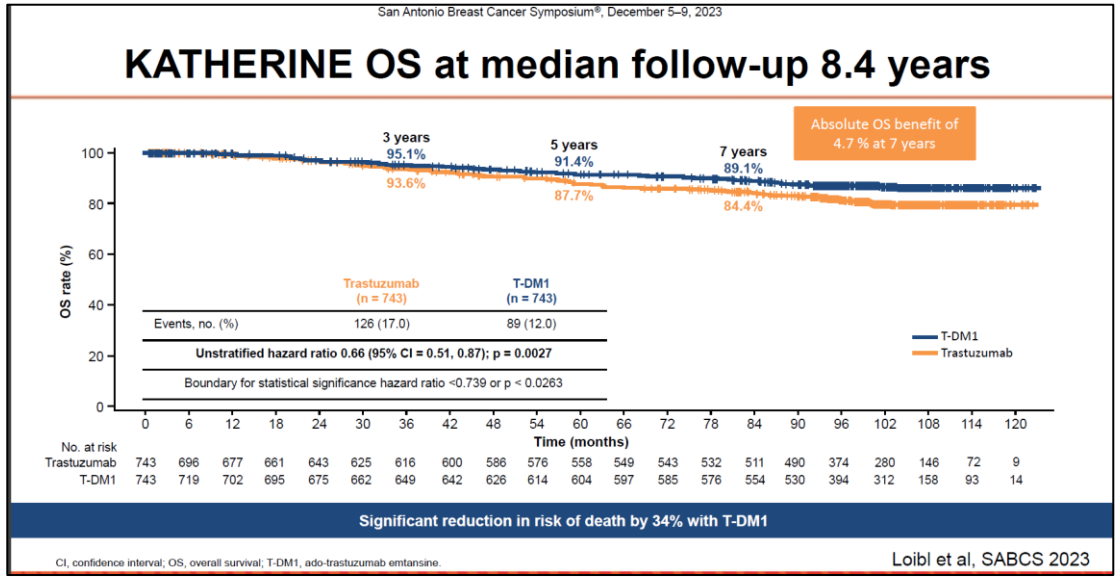
Survival with Trastuzumab Emtansine in Residual HER2-Positive Breast Cancer

Authors: Charles E. Geyer, Jr., M.D., Michael Untch, M.D., Ph.D., Chiun-Sheng Huang, M.D., Ph.D., M.P.H., Max S. Mano, M.D., Ph.D., Eleftherios P. Mamounas, M.D., M.P.H., Norman Wolmark, M.D., Priya Rastogi, M.D., +27, for the KATHERINE Study Group* Author Info & Affiliations

Published January 15, 2025 | N Engl J Med 2025;392:249-257 | DOI: 10.1056/NEJMoa2406070 | VOL. 392 NO. 3

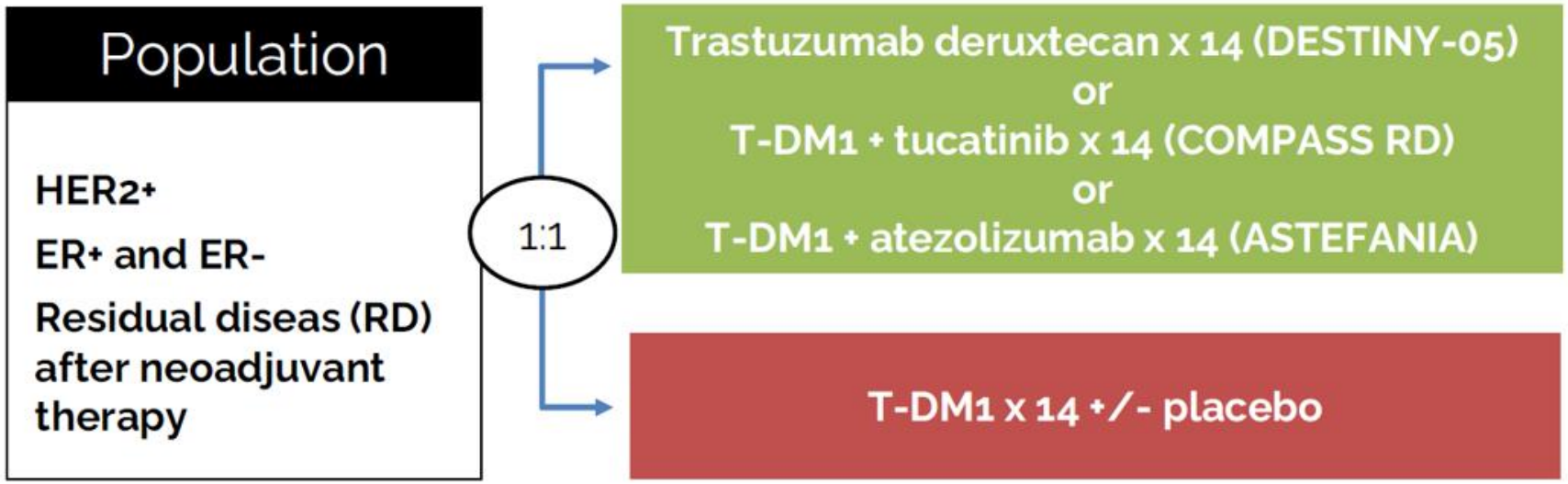






Geyer CC et al NEJM 2025

Escalation strategy

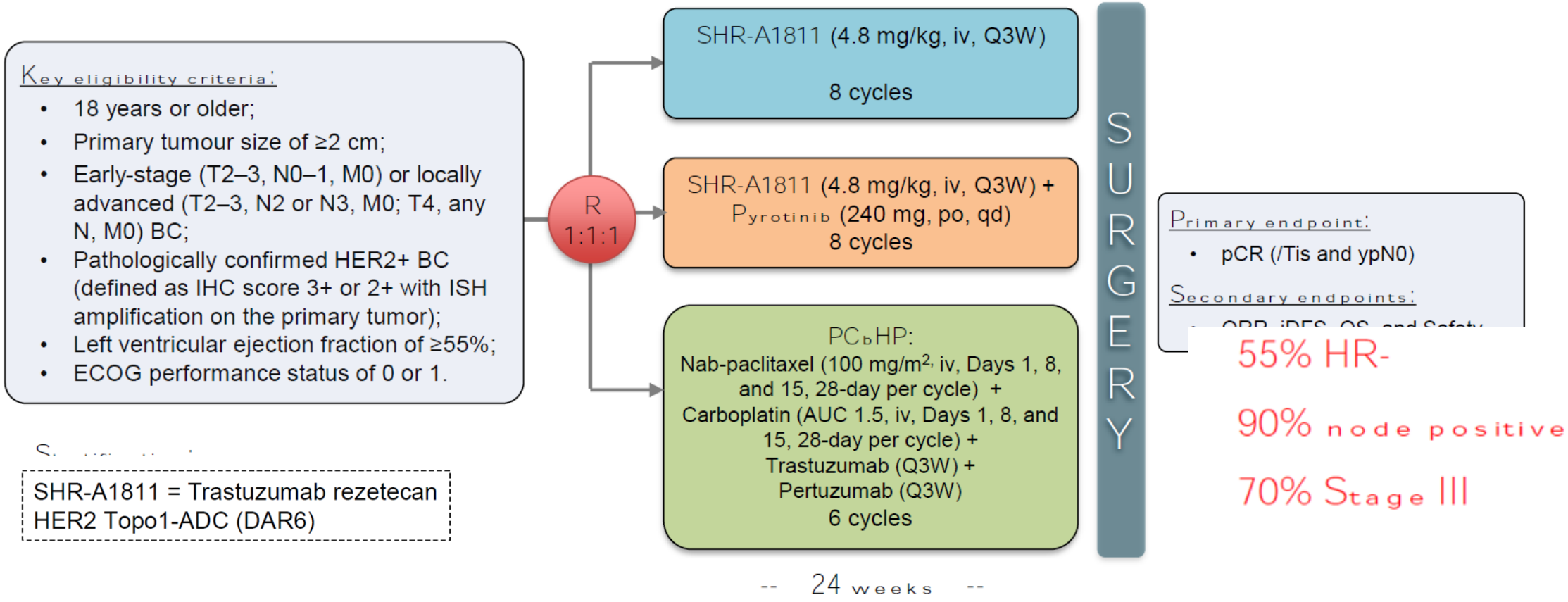


Destiny-Breast05 / COMPASS HER2 RD / ASTEFANIA

NCT04622319 NCT04457596 NCT04873362

FASCINATE N trial

HER2+ Subtype Study Design



55% HR-

90% node positive

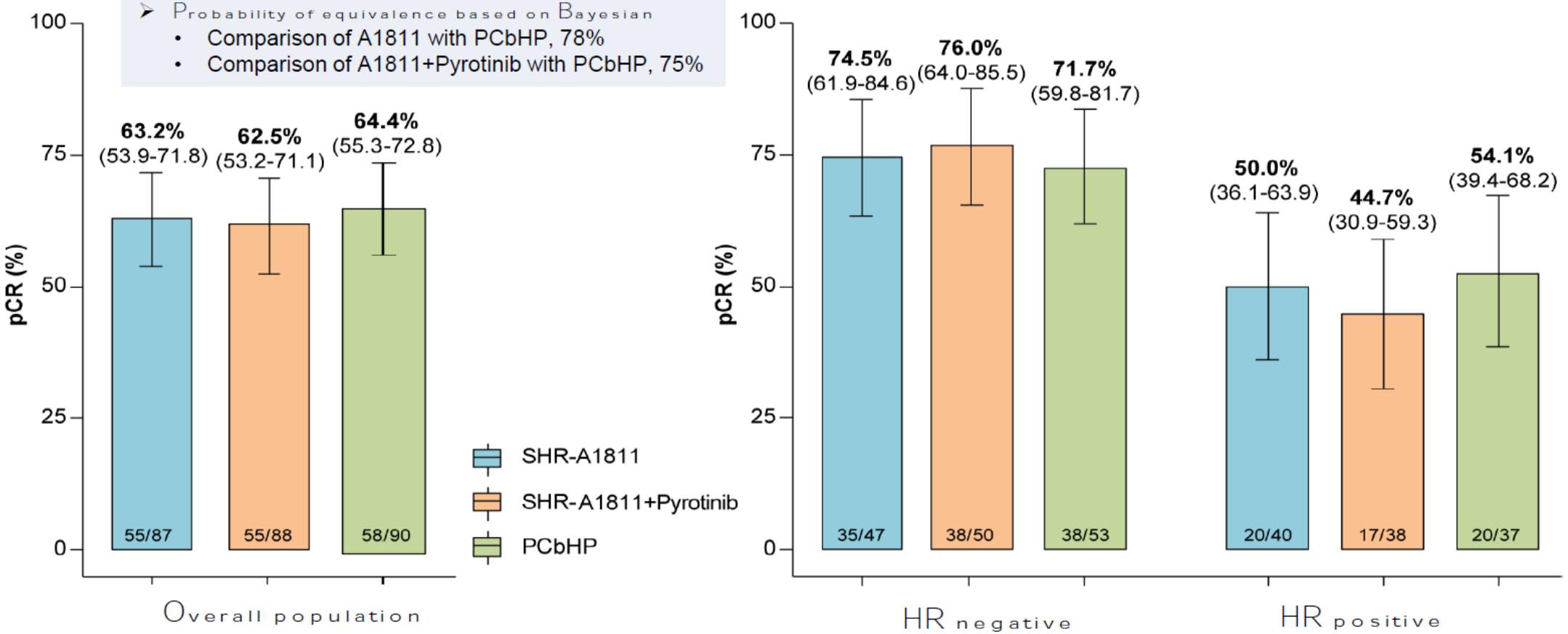
70% Stage III

Tumor assessments, including CT or MRI scans, were conducted by investigators at baseline and every two cycles thereafter until disease progression, patient withdrawal, initiation of new therapy, or death, in accordance with RECIST (version 1.1) guidelines.

Abbreviations: IHC, immunohistochemistry; ISH, in-situ hybridization; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; iDFS, invasive disease-free survival; OS, overall survival.

Efficacy Analysis: pCR

- Probability of equivalence based on Bayesian
  - Comparison of A1811 with PCbHP, 78%
  - Comparison of A1811+Pyrotinib with PCbHP, 75%



Data are % (90% CI).

There was no significant difference in pCR rate among the SHR-A1811, SHR-A1811 plus pyrotinib, and PCbHP groups

HYPOTHESIS

Potent ADC-delivered chemotherapy may overshadow dual HER2 blockade effects

Upcoming potential drug approval in early-stage HER2+ breast cancer

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Population

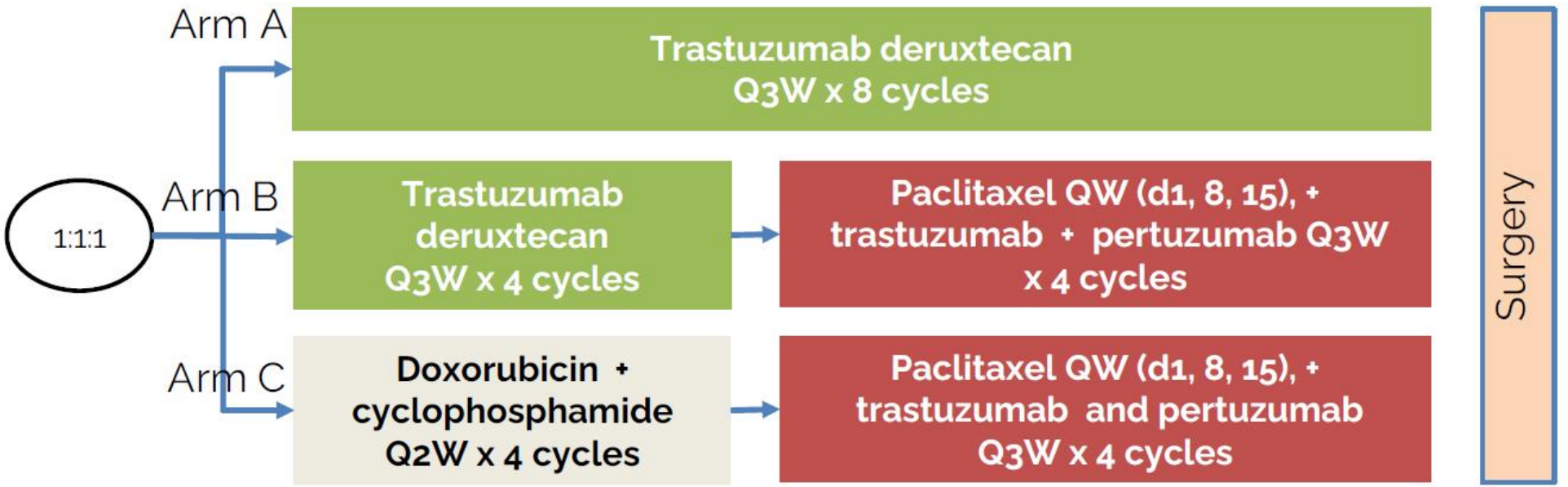
HER2+ EBC

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

NCT05113251

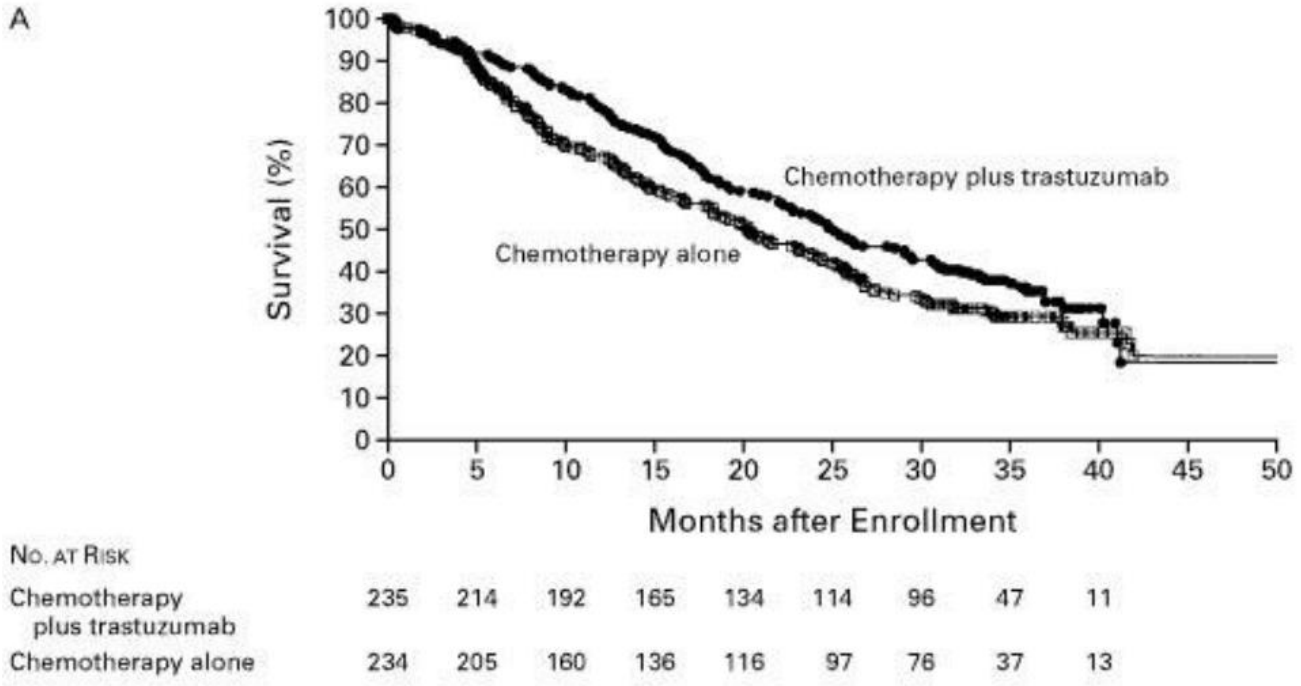


Destiny-Breast11 Phase III Trial

Harbeck N et al. SABCS 2021

First line therapy

Where were we?



<u>Design:</u>

Phase 3 RCT

AC/EC or Paclitaxel

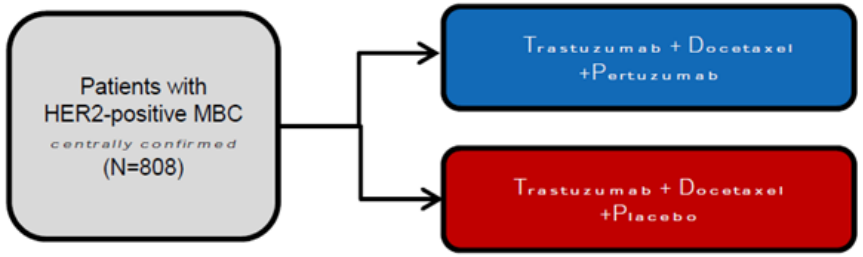
+/- trastuzumab in 1st line HER2+ MBC

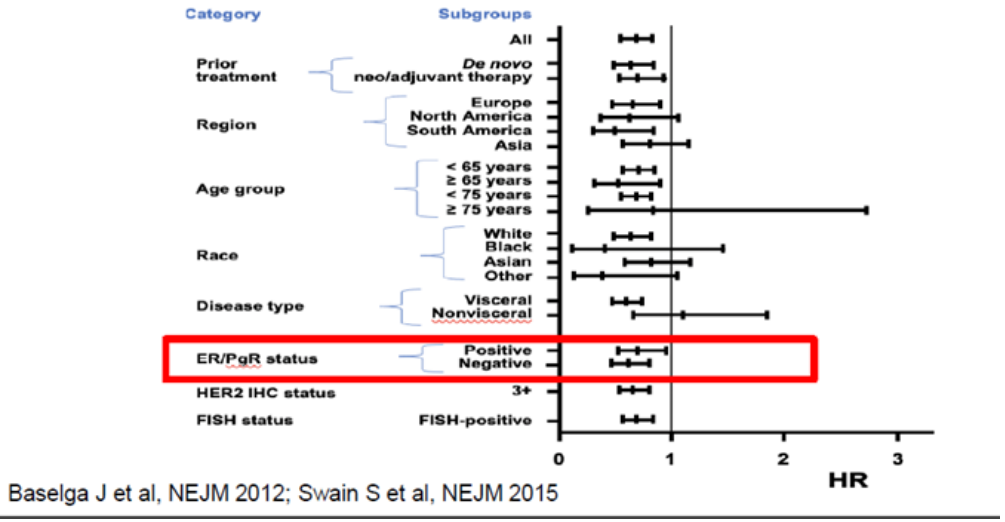
<u>Median OS:</u>

20.3 mo vs 25.1 mo (p=0.046)

Slamon D NEJM 2001

CLEOPATRA TRIAL





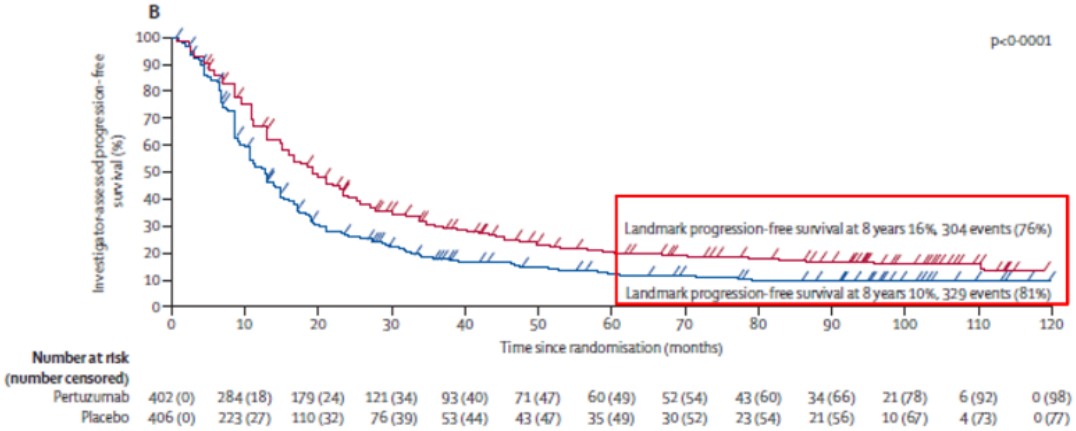
Baselga J et al, NEJM 2012; Swain S et al, NEJM 2015

1st line therapy

- Pertuzumab + trastuzumab + taxane is first line SOC

Addition of Pertuzumab Improves PFS

(median follow-up 99.9 months)

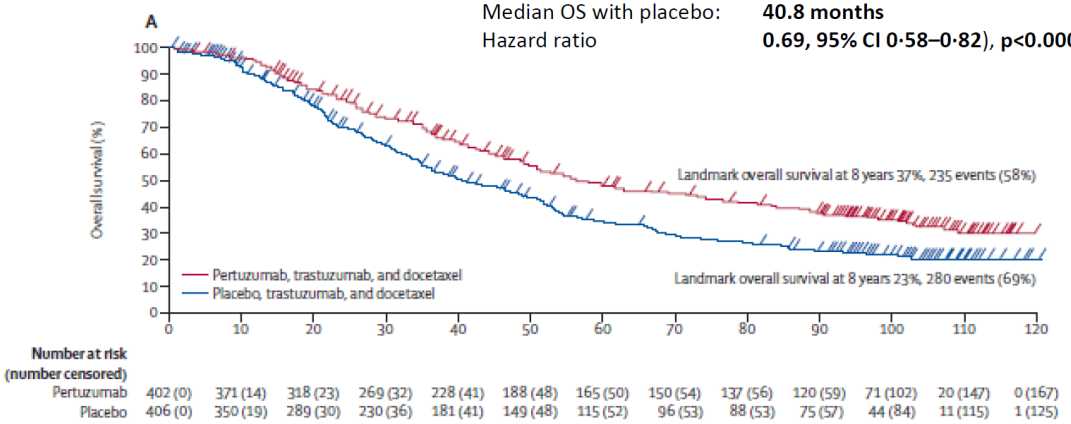


Swain S, et al. *Lancet Oncol.* 2020;21:519-530

Addition of Pertuzumab Improves Overall Survival

(median follow-up 99.9 months)

Median OS with pertuzumab: **57.1 months**
Median OS with placebo: **40.8 months**
Hazard ratio **0.69, 95% CI 0·58–0·82**), **p<0.0001**



Swain S, et al. *Lancet Oncol.* 2020;21:519-530

PHILA phase III clinical trial

SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Health San Antonio Mays Cancer Center | AACR American Association for Cancer Research

N=590

Key eligibility criteria

- HER2+ recurrent or metastatic breast cancer*
- Treatment-naive for metastatic disease
- At least one measurable lesion#
- ECOG performance status of 0 or 1
- Adequate organ function

R 1:1

Pyrotinib (400 mg, QD, orally)
Trastuzumab
Docetaxel

Placebo
Trastuzumab
Docetaxel

Primary endpoint:

✓ PFS (per INV)

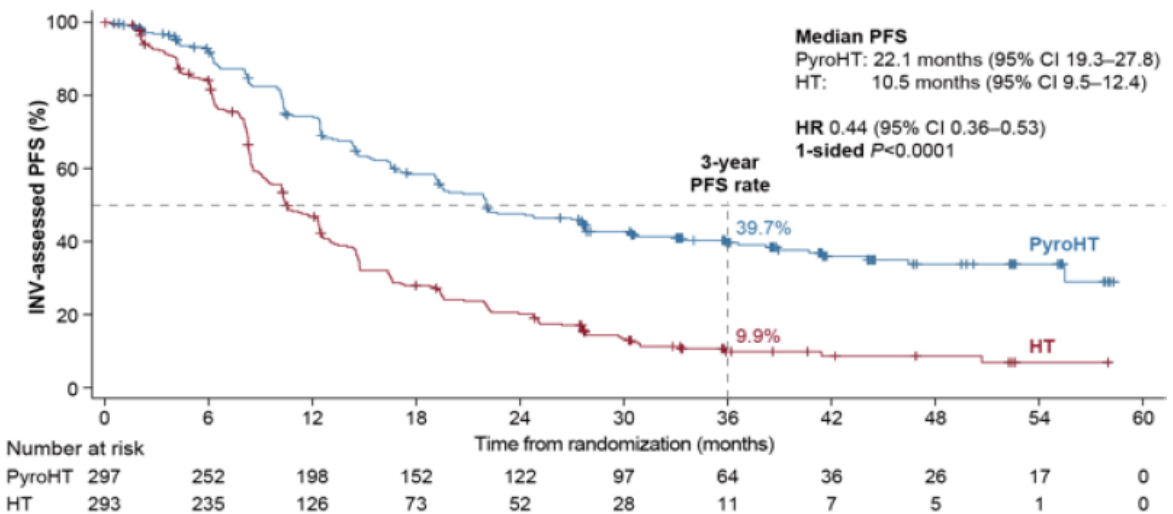
Secondary endpoints:

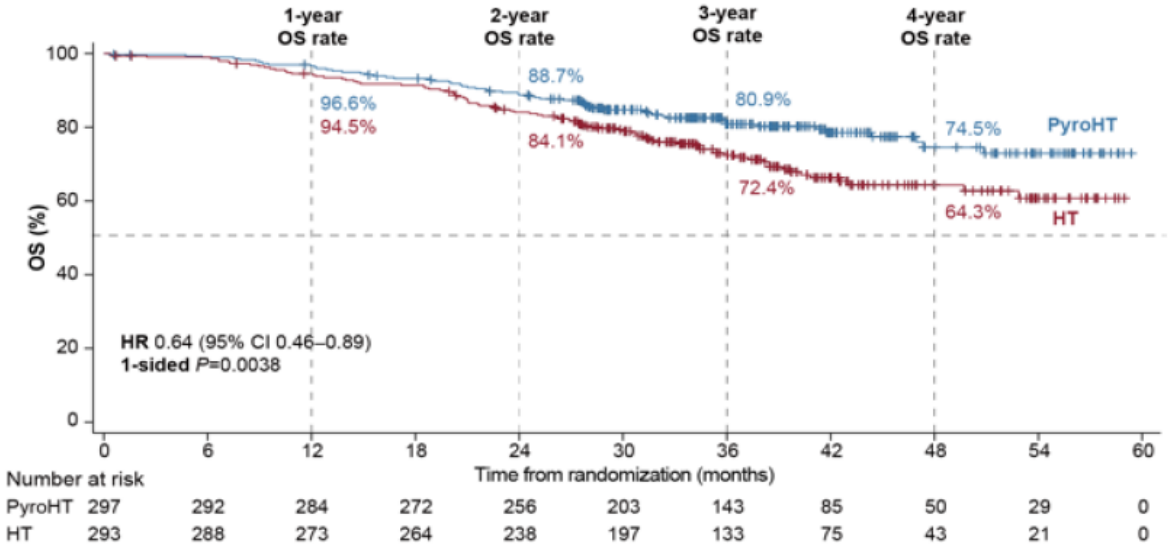
✓ PFS (per IRC)
✓ OS
✓ ORR
✓ DoR
✓ CBR‡
✓ Safety

Xu et al. SABCS 2024

Docetaxel + trastuzumab +/- pyrotinib (n=590; PHILA Phase III trial)

PFS: 22.1 vs 10.5 months





Grade ≥3 diarrhea: 47.8% vs 4.4%

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

Xu et al. SABCS 2024

How does this result compare to THP?

	PHILA	CLEOPATRA*	PERUSE**
N	**590**	**808**	**1436**
HR-positive	58%	49%	64%
HER2 3+	81%	89%	-
Visceral disease	75%	78%	69%
No previous systemic therapy	49%	53%	-
Prior trastuzumab	15%	11%	28%
Taxane + trastuzumab			
ORR	72%	69%	-
Median PFS	10.5 mo	12.4 mo	-
Taxane + dual HER2 blockade			
ORR	84%	80%	79%
Median PFS	22.1 mo	18.5 mo	20.7 mo

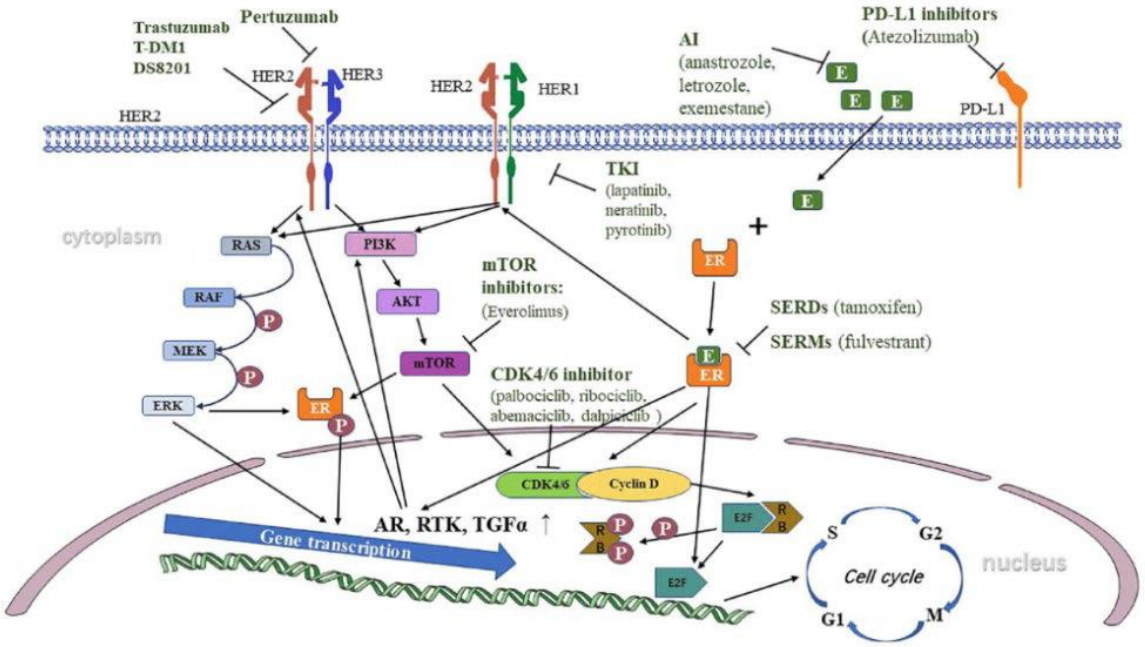
*, docetaxel; **, docetaxel, paclitaxel or nab-paclitaxel

Grade ≥3 diarrhea: 47.8% PHILA vs 7.9% CLEOPATRA

Xu et al. SABCS 2024
Baselga et al. NEJM 2012
Swain et al. Lancet Oncol. 2020
Miles et al. Ann Oncol 2021

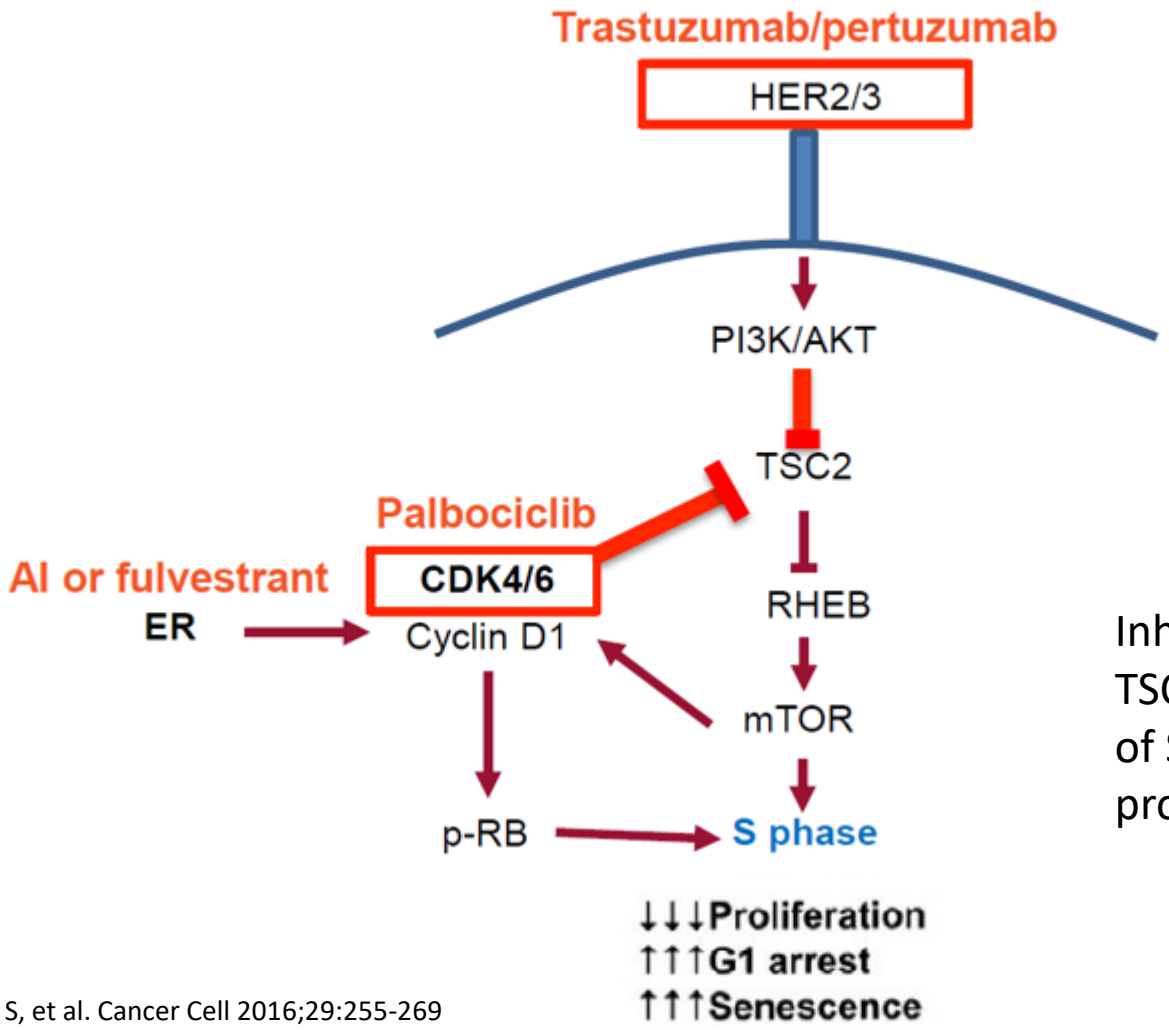
Can be done more?

Crosstalk between HER2 and ER pathways



ET ± single anti-HER2 therapy					
TAnDEM	III	Trastuzumab + anastrozole *versus* anastrozole	HR+/HER2+ (207)	4.8 *versus* 2.4 ($p = 0.0016$)	28.5 *versus* 23.9 ($p = 0.325$)
EGF30008	III	Lapatinib + letrozole *versus* letrozole	HR+/HER2+ (219)	8.2 *versus* 3.0 ($p = 0.019$)	33.3 *versus* 32.3
eLEcTRA	III	Trastuzumab + letrozole *versus* letrozole	HR+/HER2+ (57)	14.1 *versus* 3.3 ($p = 0.23$)	Data not shown
ET ± dual anti-HER2 therapy					
PERTAIN	II	Pertuzumab + trastuzumab + AI *versus* trastuzumab + AI	HR+/HER2+ (258)	18.9 *versus* 15.8 ($p = 0.007$)	60.2 *versus* 57.2
ET/CT + single anti-HER2 therapy					
SYSUCC-002	III	Trastuzumab + ET *versus* trastuzumab + CT	HR+/HER2+ (392)	19.2 *versus* 14.8 ($p < 0.0001$)	33.9 *versus* 32.5 ($p = 0.094$)

Liang Y, et al. Ther Adv Med Oncol 2024



- The cyclin D1-CDK4 axis is essential for the initiation and maintenance of growth of ErbB2-driven mammary carcinomas
- Persistent cyclin D1-CDK4 activity drives resistance to the HER2 pathway blockade

Inhibiting both CDK4/6 and HER2 maximizes suppression of TSC2 phosphorylation, leading to a more complete shutdown of S6RP phosphorylation and inhibition of Rb, reducing cellular proliferation.

Goel S, et al. Cancer Cell 2016;29:255-269

AFT-38 PATINA

Pre-Study

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

Key eligibility criteria

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

N=518

R* 1:1

Palbociclib (125 mg PO QD D1-D21)
Trastuzumab ± Pertuzumab + Endocrine therapy†

Trastuzumab ± Pertuzumab + Endocrine therapy†

Until PD or toxicity

SURVIVAL FOLLOW-UP

Start of Study AFTER Induction
Patients who experienced disease progression during induction or screening were not included in study. Patients with *de novo* resistance were eliminated

Metzger O et al. SABCS 2024

AFT-38 PATINA Study Design

Pre-Study

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

Key eligibility criteria

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

N=518

R* 1:1

- **Palbociclib (125 mg PO QD D1-D21) Trastuzumab ± Pertuzumab + Endocrine therapy†**
- **Trastuzumab ± Pertuzumab + Endocrine therapy†**

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification Factors

- Pertuzumab Use (Yes vs. No)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (Yes vs. No, including denovo)*
- Response to induction therapy (CR or PR vs. SD) by investigator assessment*
- Type of endocrine therapy (Fulvestrant vs. AI)

97% used pertuzumab

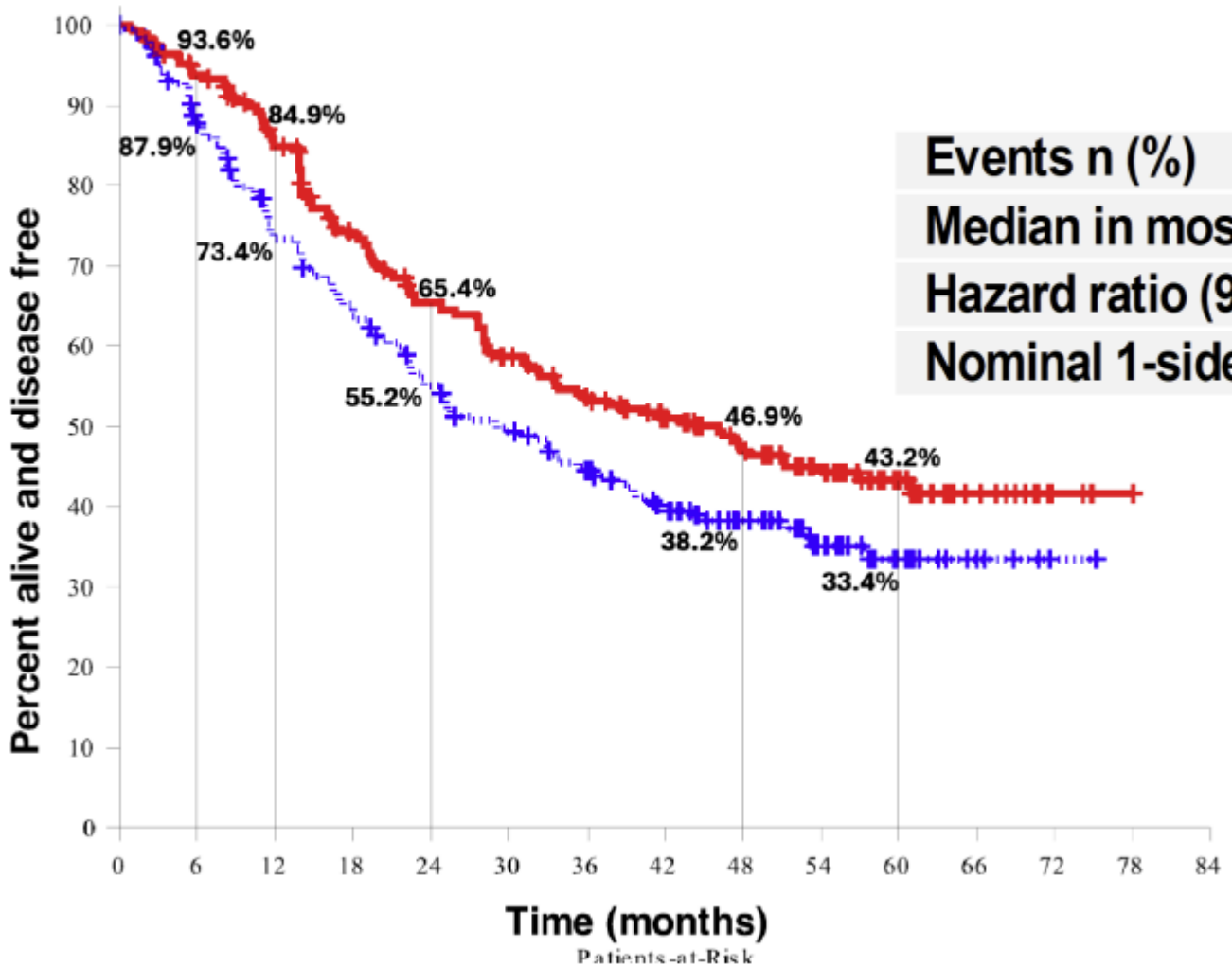
Prior trastuzumab 71%

ORR 69%

AI: 91%

Metzger O et al. SABCS 2024

Investigator-Assessed PFS



	Palbo + Anti-HER2 and ET	+ Anti-HER2 and ET
Events n (%)	126/261	136/257
Median in mos (95% CI)	44.3	29.1
Hazard ratio (95% CI)	0.74 (0.58–0.94)	
Nominal 1-sided *P* value	0.0074	

This is quite high!

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

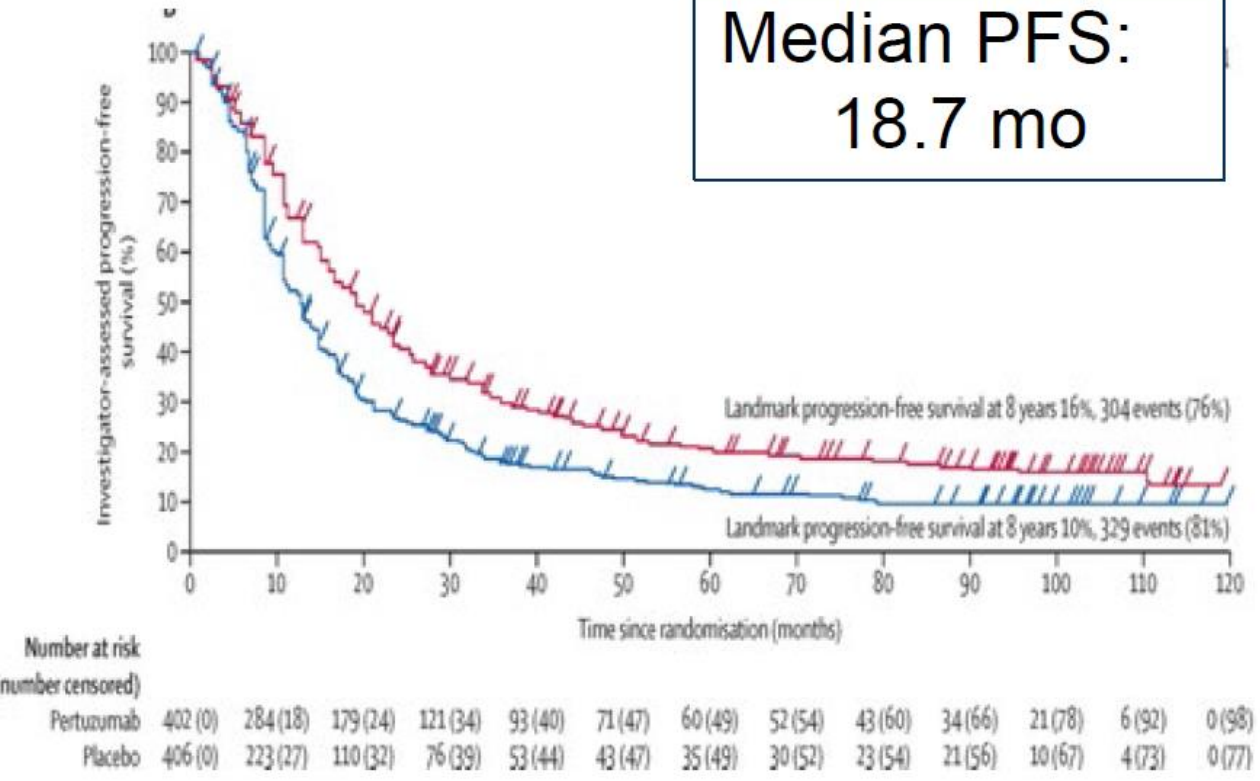
Metzger O et al. SABCS 2024

CLEOPATRA End-of-Study Results:

Adding Pertuzumab to Taxane + Trastuzumab Improves PFS and OS

(median follow-up ~100 months)

Median PFS:
18.7 mo



90% of patients never had prior trastuzumab so PFS should be higher with CLEOPATRA than in PATINA, where 71% had prior trastuzumab

Why is this PFS so much lower than the control arm in PATINA?

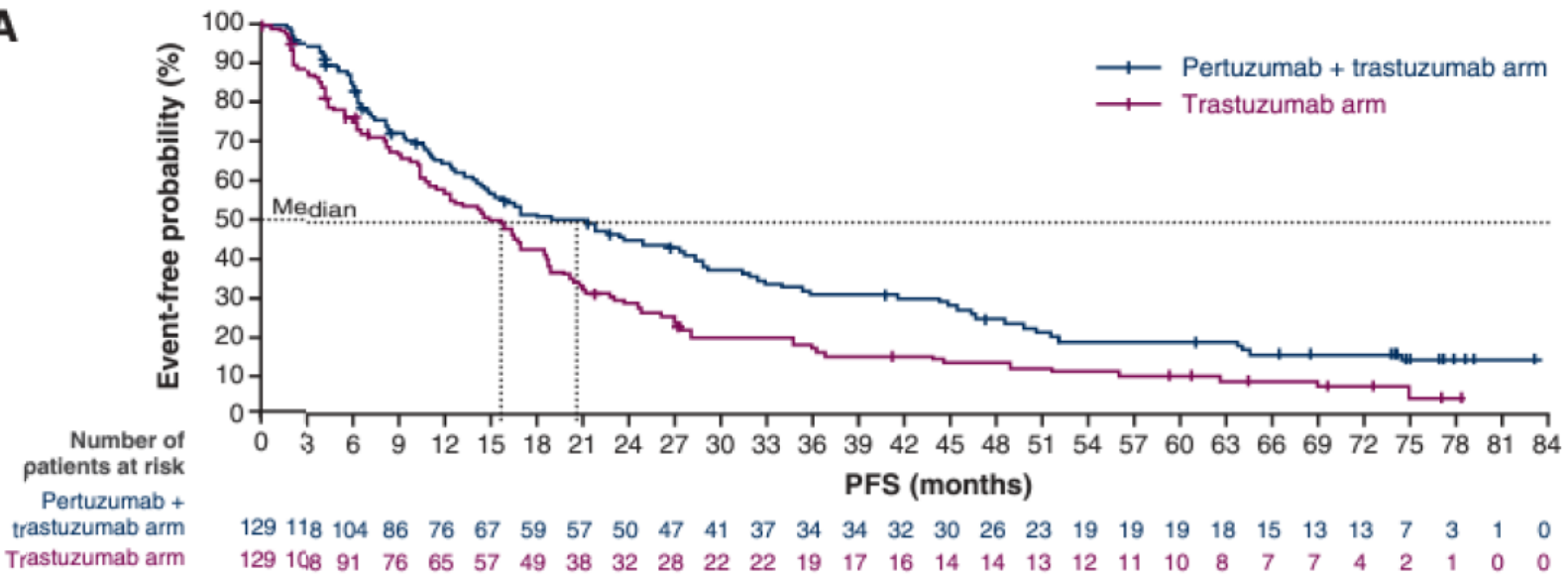
Endocrine therapy was not allowed during maintenance setting in CLEOPATRA

Swain S, et al. Lancet Oncol. 2020;21:519-530.

PERTAIN End-of-Study Results:
Adding Pertuzumab to Trastuzumab and Aromatase Inhibitor (induction chemo per investigator choice)

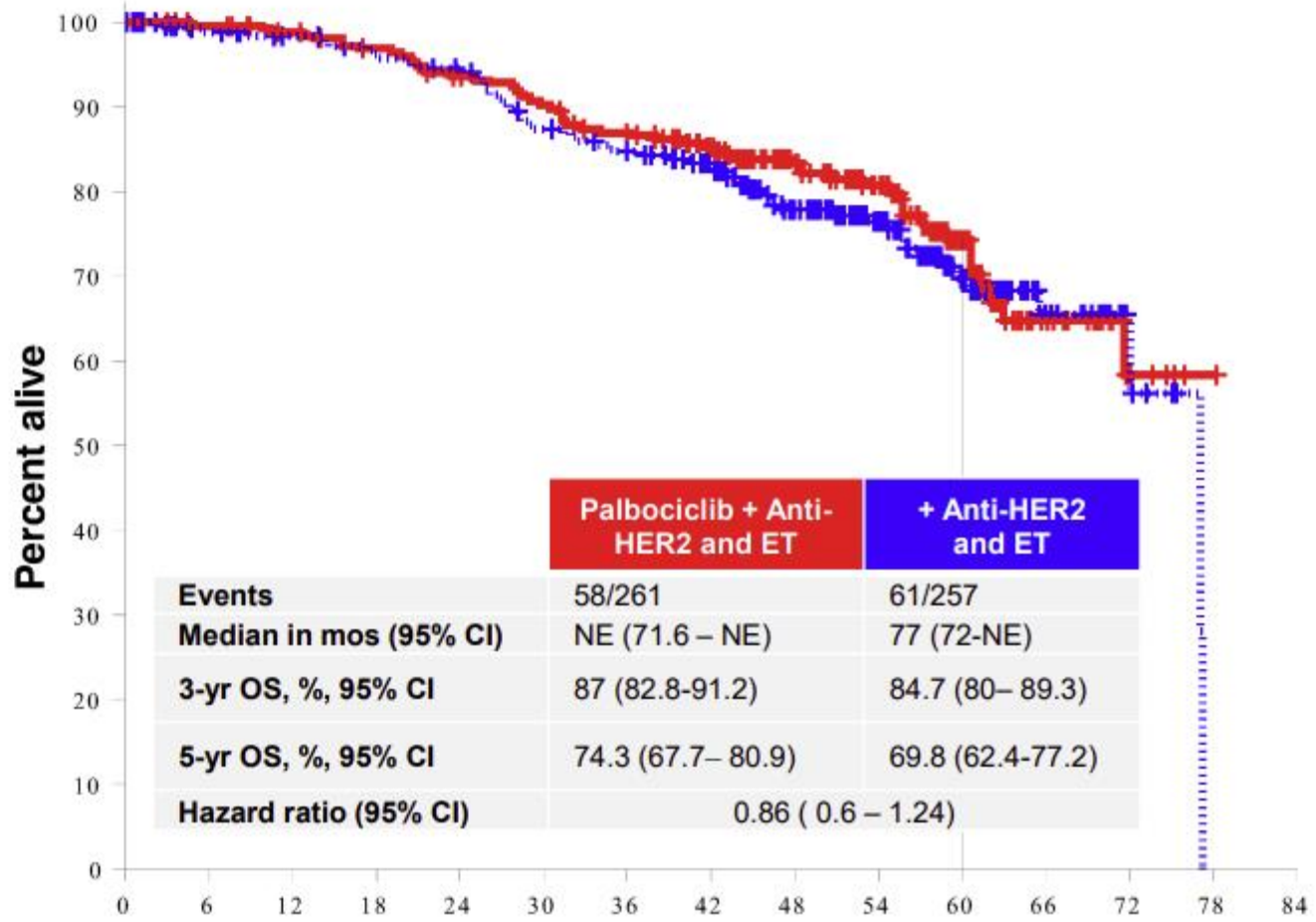
Median PFS: 20.6 mo with pertuzumab
(16.9 mos with chemo; 26.6 mos without chemo)

72% of patients had no prior trastuzumab
Endocrine therapy used by all in this study



Arpino G, et al. Clin Cancer Res. 2023;29:1468-76.

Secondary endpoint: Overall Survival (interim analysis)



	Palbociclib + Anti-HER2 and ET	+ Anti-HER2 and ET
Events	58/261	61/257
Median in mos (95% CI)	NE (71.6 – NE)	77 (72-NE)
3-yr OS, %, 95% CI	87 (82.8-91.2)	84.7 (80– 89.3)
5-yr OS, %, 95% CI	74.3 (67.7– 80.9)	69.8 (62.4-77.2)
Hazard ratio (95% CI)	0.86 (0.6 – 1.24)	

Final overall survival analysis requires 247 events. Only 119 observed thus far.

*Kaplan-Meier method; †Unstratified Cox model; CI=confidence interval; NE=not evaluable; OS=overall survival;

(Grade ≥ 2 in ≥10% of patients)

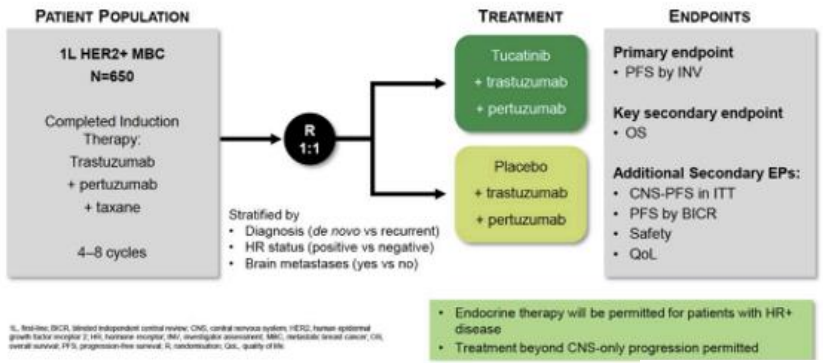
Adverse Events, n (%)*	**Palbociclib (N= 261)**			**Control (N= 248)**		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Neutropenia	52 (19.9)	165 (63.2)	12 (4.6)	10 (4.0)	11 (4.4)	0 (0.0)
White blood cell count decreased	30 (11.5)	30 (11.5)	1 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)
Fatigue	60 (22.9)	14 (5.4)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

- The incidence of Grade ≥4 AEs regardless of treatment attribution was similar across study arms (12.3% vs. 8.9% for palbociclib-containing arm vs. control; p-value = 0.21)
- No treatment-related deaths were reported in either arm of the study

*AEs were assessed per CTCAE V4.0 regardless of treatment attribution. Stomatitis, mouth ulceration, mucosal inflammation, and mucositis were assessed as medical concepts using grouped terms. Fatigue and asthenia were assessed as medical concepts using grouped terms. Cardiac safety data was also included in the table above.
AE=adverse events.

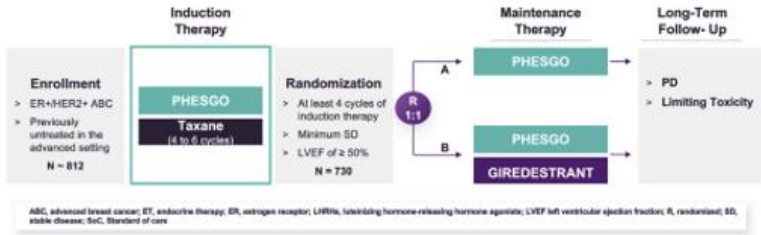
Can be done more in first line?

HER2CLIMB-05: Study design



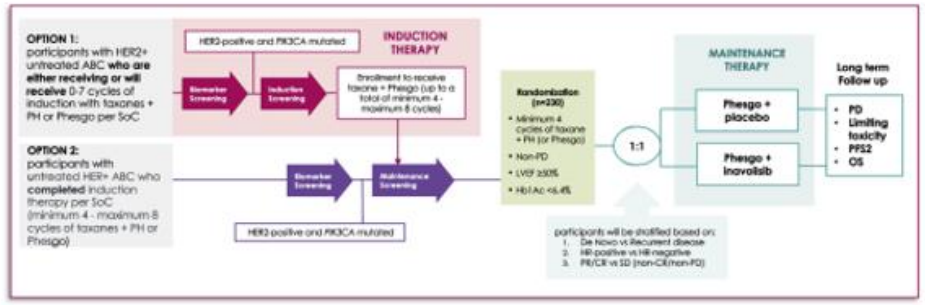
HEREDERA TRIAL: A role for ORAL SERDs IN 1st LINE?

A PHASE III, RANDOMIZED, OPEN-LABEL STUDY EVALUATING THE EFFICACY AND SAFETY OF GIREDESTRANT IN COMBINATION WITH PHESGO VERSUS PHESGO AFTER INDUCTION THERAPY WITH PHESGO+ TAXANE IN PATIENTS WITH PREVIOUSLY UNTREATED HER2-POSITIVE, ESTROGEN RECEPTOR-POSITIVE LOCALLY-ADVANCED OR METASTATIC BREAST CANCER



INAVO 122 TRIAL: A role for PI3K inh in 1st LINE?

Phase III, randomized, double-blind, placebo-controlled study designed to compare efficacy and safety of Inavolisib in combination with Phesgo



Front Line Standard is Likely to Change: T-DXd?

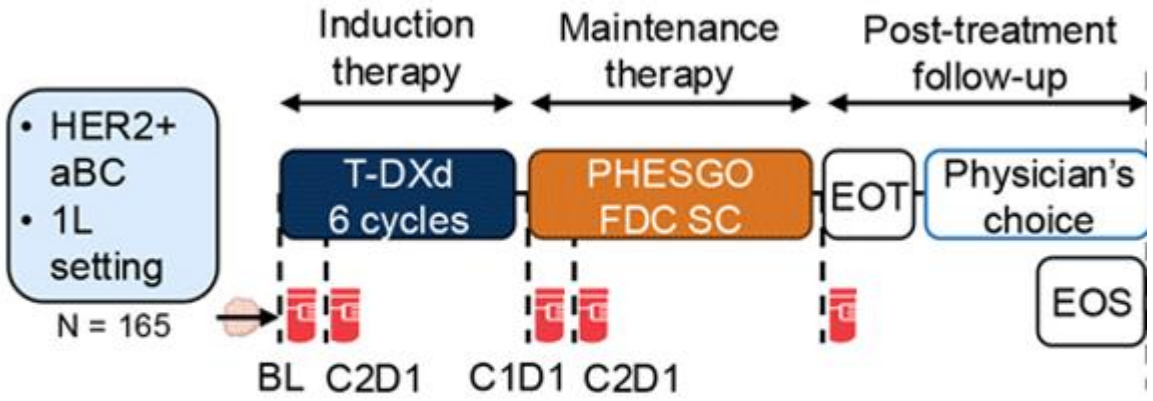
DESTINY-Breast09: Is T-DXd superior to THP in first-line setting?

How will QOL on T-DXd compare to maintenance HP?

NCT04784715.

Primary endpoint: PFS

DEMETHER: T-DXd Induction



Primary endpoints: 1-year PFS; 3-year OS

Development of shorter or non-continuous, more tolerable, and sustainable trastuzumab deruxtecan schedules?

Second line therapy and beyond

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

An open-label, multicenter study (NCT03529110)

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

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

R 1:1

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

Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

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

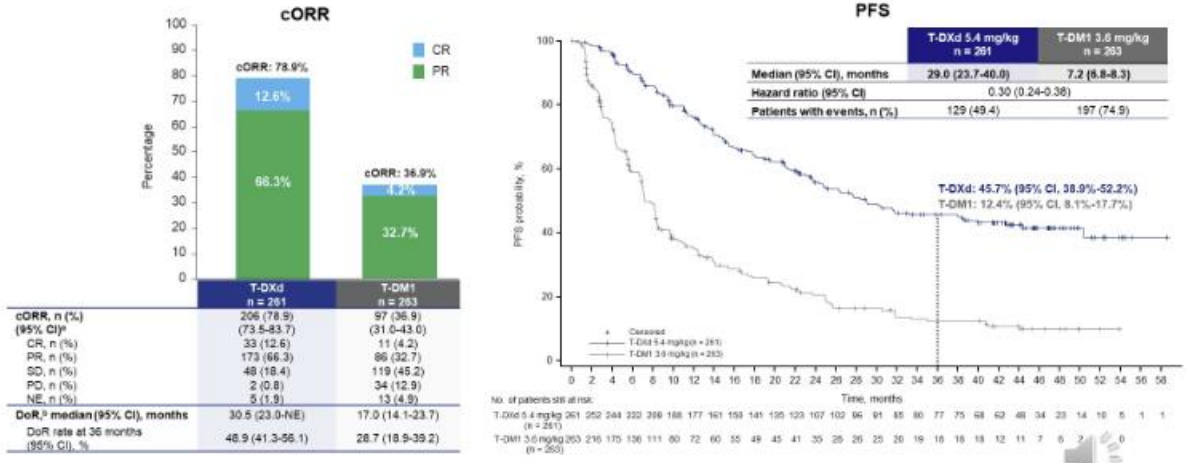
Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

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

> **> CLEOPATRA (18.5 m) and > MARIANNE (14. 1 m) trials**

Updated data at ASCO 2024

Efficacy by investigator assessment



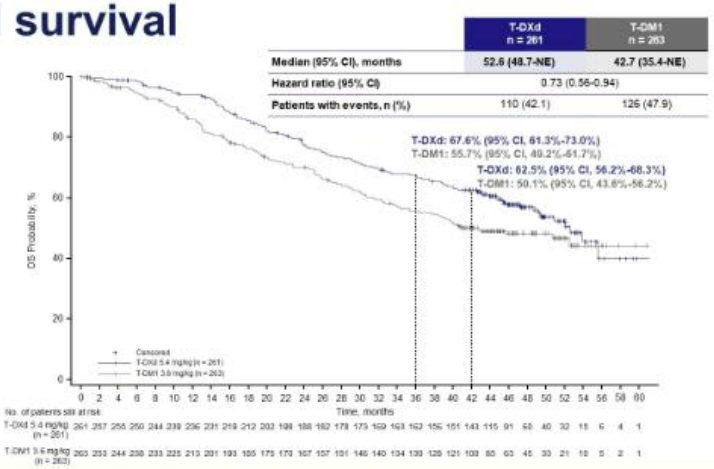
cORR, confirmed objective response rate; CR, complete response; DoR, duration of response; NE, not estimable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Based on Clopper-Pearson method for single proportion and for the difference of 2 proportions with continuity correction. [b]Median is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method.

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Erika Hamilton, MD

Δ mPFS: 22 months

DESTINY-Breast03: Updated Analysis (DCO Nov 20, 2023)

Overall survival



The risk of death was reduced by 27% for patients receiving T-DXd compared with those receiving T-DM1

OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Erika Hamilton, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

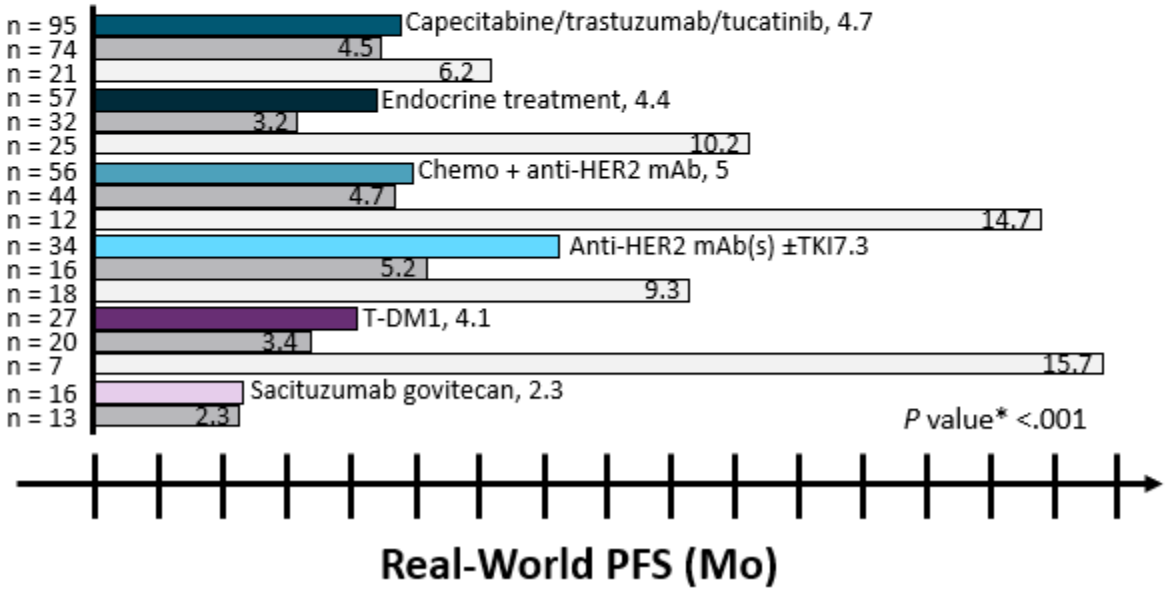
These data continue to support the use of T-DXd as standard of care in patients with HER2-positive mBC whose disease progressed after trastuzumab and taxane and show the longest OS observed in this setting

Cortes J et al Nat Med 2024

Evidence for Treatment After T-DXd in MBC

Real-world retrospective study of non-T-DXd tx immediately after T-DXd[1]:

- N = 352 patients with HER2+ MBC
- Median 4L of therapy prior to T-DXd



Multicenter cohort study of tucatinib + trastuzumab + capecitabine with prior T-DXd[2]:

- N = 101 patients with HER2+ MBC
- Median 4L of prior therapy for MBC

Outcomes, mo (95% CI)	All Patients (n = 101)	Patients With BM (n = 39)
mPFS	4.7 (3.9-5.6)	5.0 (3.9-6.8)
mOS	13.4 (11.1-NR)	12.9 (9.6-NR)
mTTNT	5.2 (4.5-7.0)	5.7 (4.7-8.6)

Progression on prior T-DXd
Discontinued prior T-DXd in the absence of progression

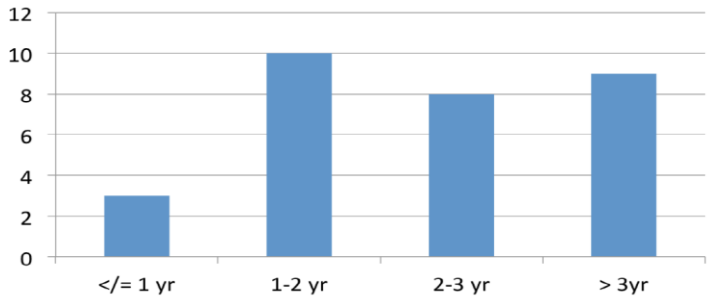
Treatments are ordered by prevalence
*Log-rank test to compare real-world PFS among all treatment types

1. Tarantino. SABCS 2024. Abstr P1-08-08. 2. Frenel. JAMA Netw Open. 2024;7:e244435.

Brain metastases

CNS Disease is Frequent in HER2+ MBC

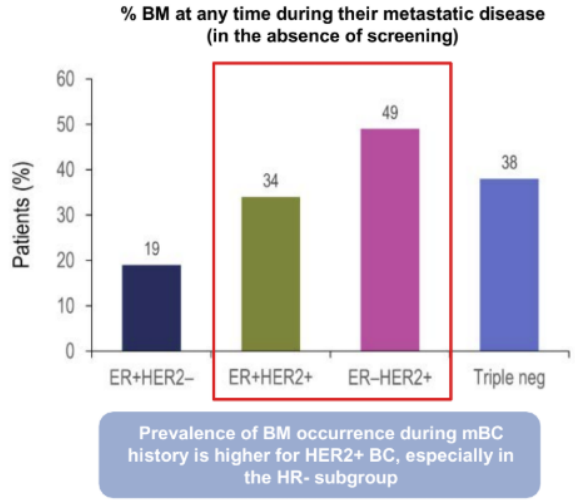
- 30-50% incidence—risk continues over time



Of N=64 patients alive ≥3 yrs from HER2+ MBC diagnosis, the number of patients who developed new brain metastases in each time interval

Olson et al, under review; Brufsky et al, CCR 2011; Lin et al, JCO 2008; Lin et al, CCR 2009; Boccardo et al, ASCO 2008; Sutherland et al. Br J Ca 2010: Metro et al. Ann Oncol 2011: Lin et al J Neurooncol 2011: Bachelot et al. ASCO 2011

Brain Metastases in HER2+ Breast Cancer



Darlix A, Br J Cancer 2020; Pasquier D, et al. Eur J Cancer 2020; Le Rhun et al, Ann Oncol 2021

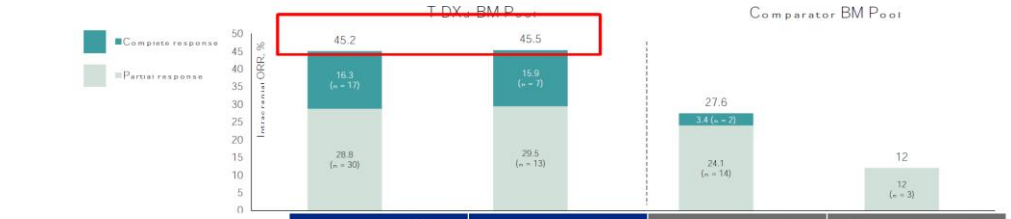
Destiny Breast 01, 02, 03 pooled analysis

MADRID 2023 ESMO congress

DESTINY-Breast01, -02, and -03

Exploratory Best IC Response, ORR, and DoR per BICR

Intracranial ORR[a]

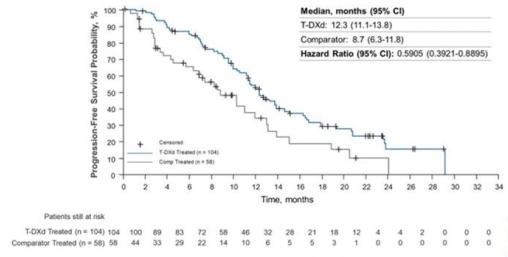
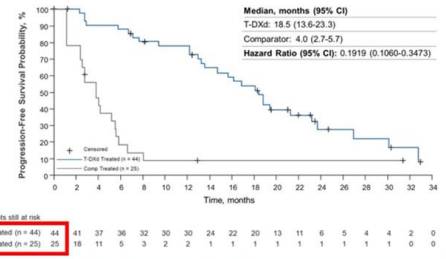


	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)	Treated/stable BMs (n = 58)	Untreated/active BMs (n = 25)
Best overall IC response, n (%)				
Stable disease	48 (46.2)	15 (34.1)	28 (48.3)	15 (60.0)
Progressive disease	3 (2.9)	1 (2.3)	7 (12.1)	5 (20.0)
Not evaluable/Missing	6 (5.8)	8 (18.2)	7 (12.1)	2 (8.0)
IC-DoR, median, months (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)	11.0 (5.6-16.0)	NA[b]

- 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; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.
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.
[a]IC-ORR was assessed per RESIST v1.1. [b]IC-DoR NA due to small number of responders (n < 10).

DB01/02/03: CNS-PFS with T-DXd in HER2+ BM

Treated/Stable Brain Metastases	Untreated/Active Brain Metastases
	
HR 0.59 (95% CI, 0.39-0.89) Median CNS-PFS: 12.3 vs. 8.7 months	**HR 0.19** (95% CI, 0.11-0.35) Median CNS-PFS: 18.5 vs. 4.0 months

Hurvitz SA et al. ESMO 2023.

Numerically longer median CNS-PFS was observed in patients with treated/stable and active BMs randomized to T-DXd vs comparator

Stable: treated with local modalities and non-progressive

Active: either untreated asymptomatic *or* treated with local modalities but progressive

Per FDA criteria, patients with untreated BMs from DESTINY-Breast02 and -03 would be considered to have active BMs[5]

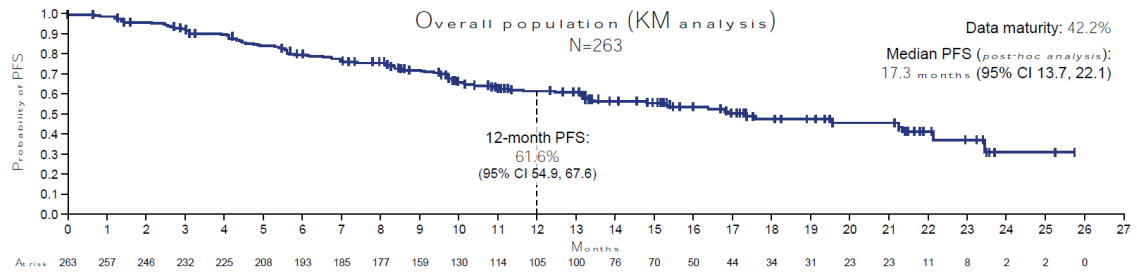
- The population of patients with baseline BMs from DESTINY-Breast02 and -03 therefore consists of a mix of treated/stable and untreated/active metastases

Sara A. Hurvitz, MD

DESTINY-Breast12

Baseline BMs: PFS (primary endpoint)

DESTINY-Breast12

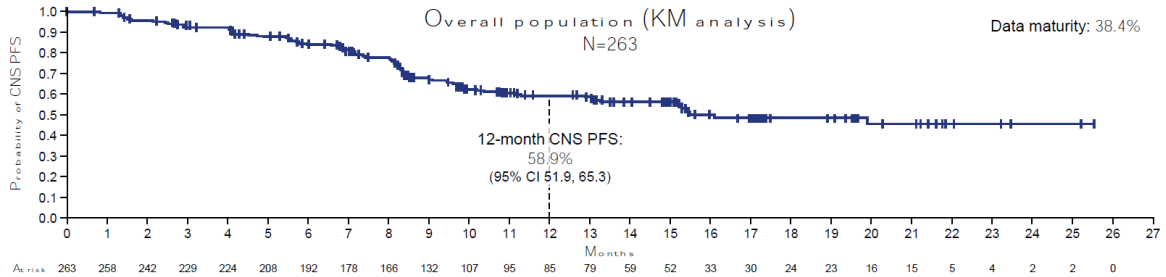


	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)	Active BM subgroups: Untreated (n=39) Post-hoc analysis	Active BM subgroups: Previously treated / progressing (n=67) Post-hoc analysis
Overall no. events	111	64	47	20	27
12-month PFS, % (95% CI)	61.6 (54.9, 67.6)	62.9 (54.0, 70.5)	59.6 (49.0, 68.7)	47.0 (29.6, 62.7)	66.7 (53.4, 76.9)

T-DXd showed consistent 12-month PFS in patients with stable and active BMs

Baseline BMs: CNS PFS

DESTINY-Breast12

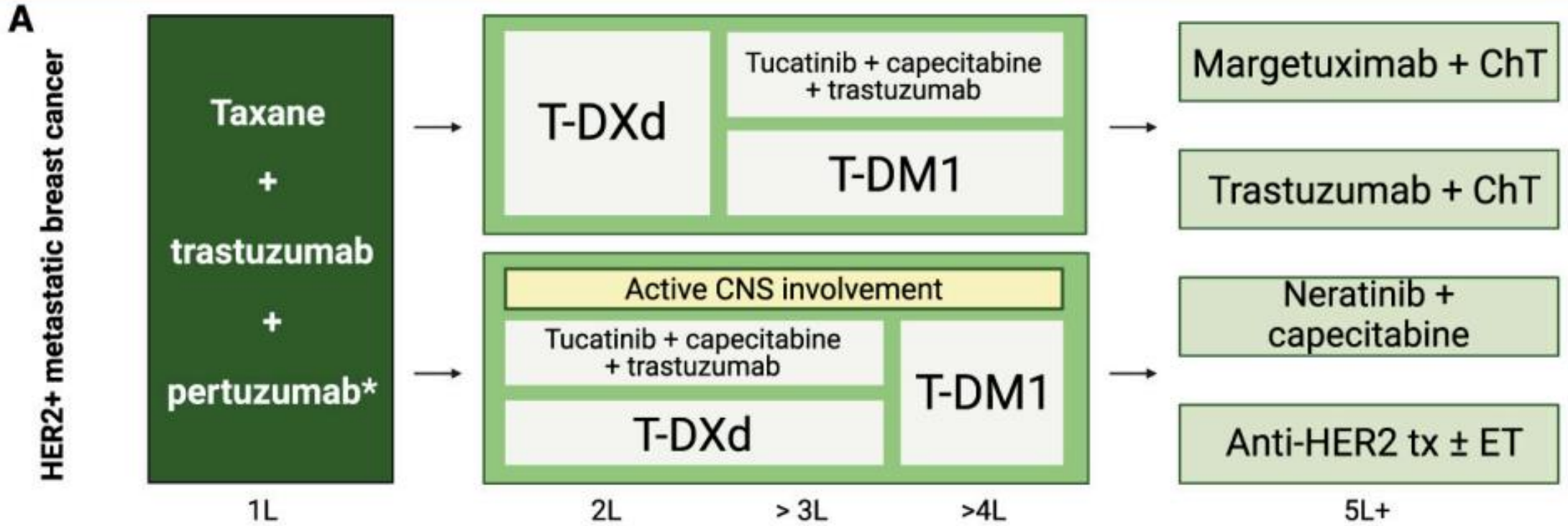


	Overall population (N=263)	Stable BMs (n=157)	Active BMs (n=106)
Overall no. events	101	61	40
12-month CNS PFS, % (95% CI)	58.9 (51.9, 65.3)	57.8 (48.2, 66.1)	60.1 (49.2, 69.4)

T-DXd showed consistent 12-month CNS PFS in patients with stable and active BMs

Lin NU ESMO 2024; Harbeck. Nature Medicine. 2024;30:3717.

HER2+ MBC Treatment Algorithm



* After induction chemotherapy, maintenance therapy with ET and CDK4/6 with HP indicated for ER pos disease

Chiara Corti et al., Systemic Therapy in Breast Cancer. Am Soc Clin Oncol Educ Book 44, e432442(2024).DOI:10.1200/EDBK_432442