Atlanta Breast Cancer CONFERENCE

How Do I Treat HER2+ Breast Cancer

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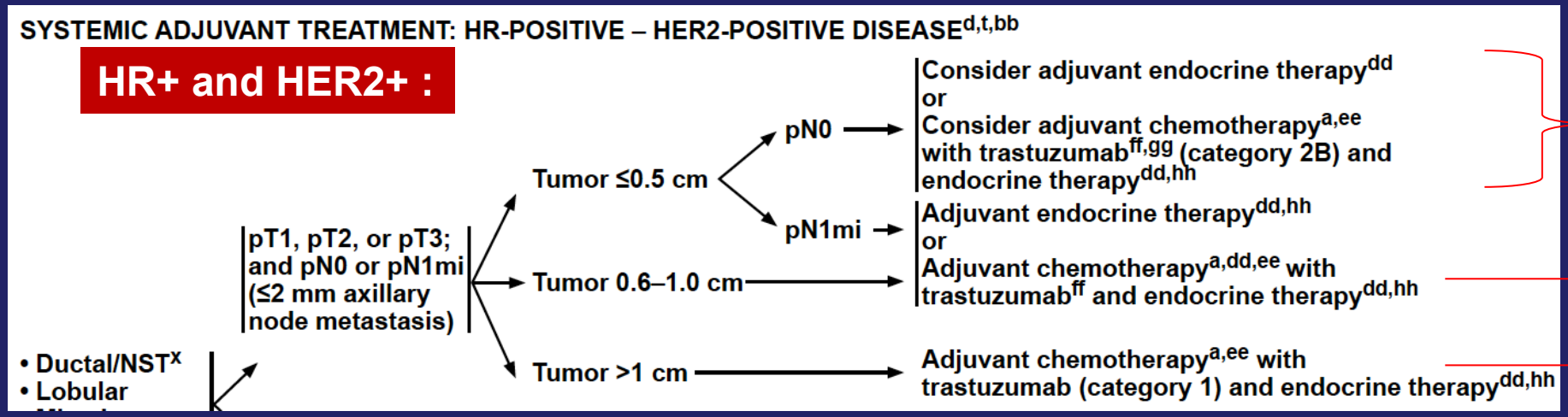
Fred Hutchinson Cancer Center

Partners for Advancing Clinical Education

Bio Ascend™

Small node negative (cT1a/T1b)

NCCN Guidelines 2024: Stage I

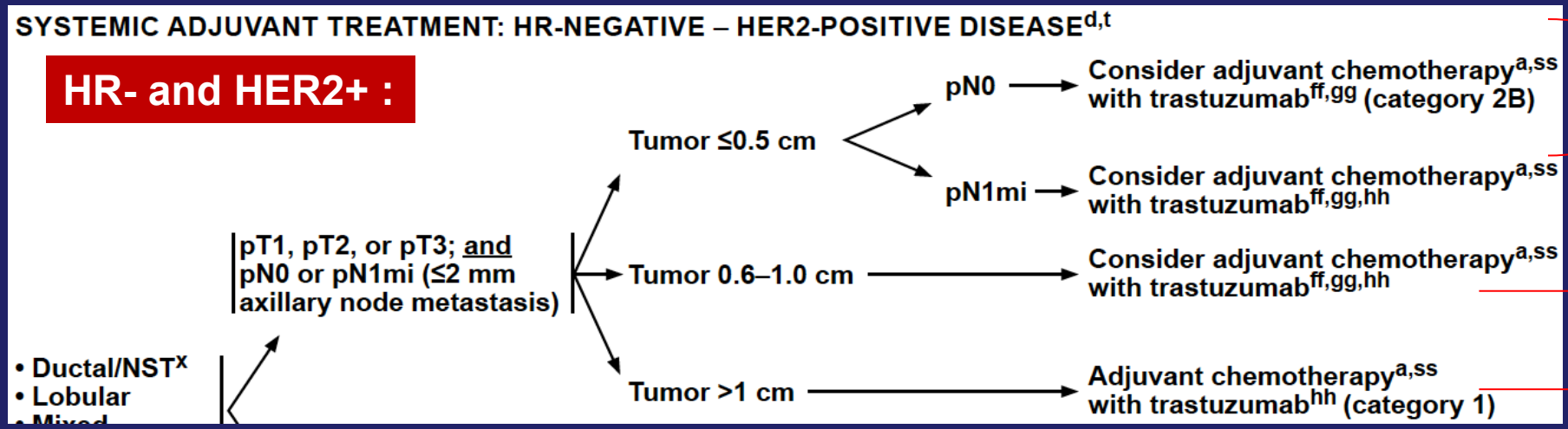


31%

62%

70%

Receipt of chemo 2010-19 SEER Database Analysis



42%

72%

77%

Receipt of chemo 2010-19 SEER Database Analysis

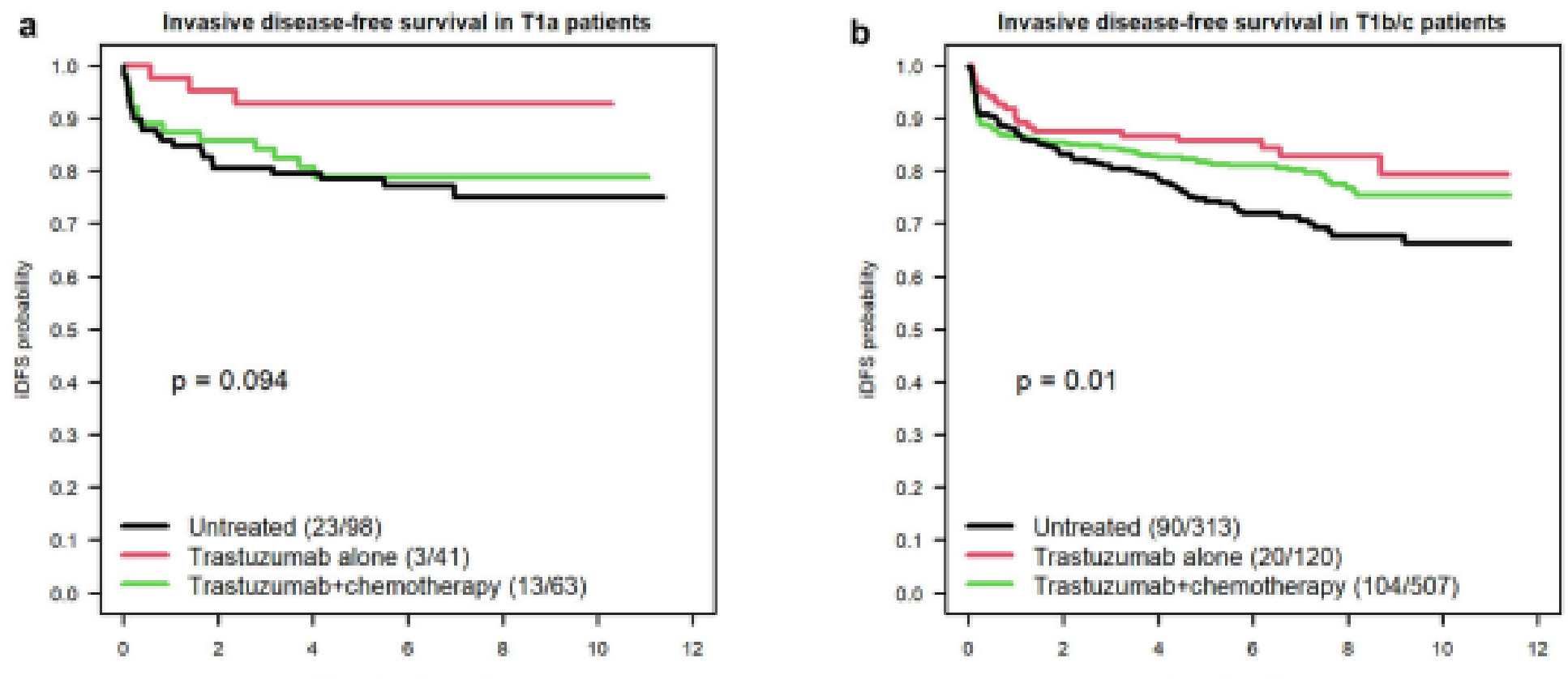
Waks A, et al. *Cancer*. 2025;131:e35729

SEER 2010-19 Stage IA HER2+ 7-year Breast Cancer Specific Survival, N=12896

HR Positive 74%	Overall N-9547	pT1mi N-504	pT1a N-1479	pT1b N-2441	pT1c N-5123
Yes Chemo	97.9 (N=5625)	100.0 (N=59)	98.7 (N=453)	98.8 (N=1522)	97.5 (N-3591)
No Chemo	96.6 (N=3922)	99.1 (N=445)	98.9 (N=1026)	97.6 (N=919)	93.7 (N=1532)
Adj HR Adj p-value	0.60 0.009	Not Reported	Not Reported	.068 0.426	0.60 0.02
HR Negative 26%	**Overall N-3349**	**pT1mi N-492**	**pT1a N-730**	**pT1b N-712**	**pT1c N-1415**
Yes Chemo	96.3 (N=1976)	100.0 (N=69)	97.2 (N=303)	97.4 (N=514)	95.4 (N-1090)
No Chemo	96.0 (N=1373)	97.8 (N=423)	97.7 (N=427)	96.5 (N=198)	91.0 (N=325)
Adj HR Adj p-value	0.70 0.19	Not Reported	Not Reported	Not Reported	0.61 0.137

Waks A, et al. *Cancer*. 2025;131:e35729

Outcomes T1a-b HER2+ 2010-21
Multi-Institutional Retrospective Analysis ASCO LinQ Database



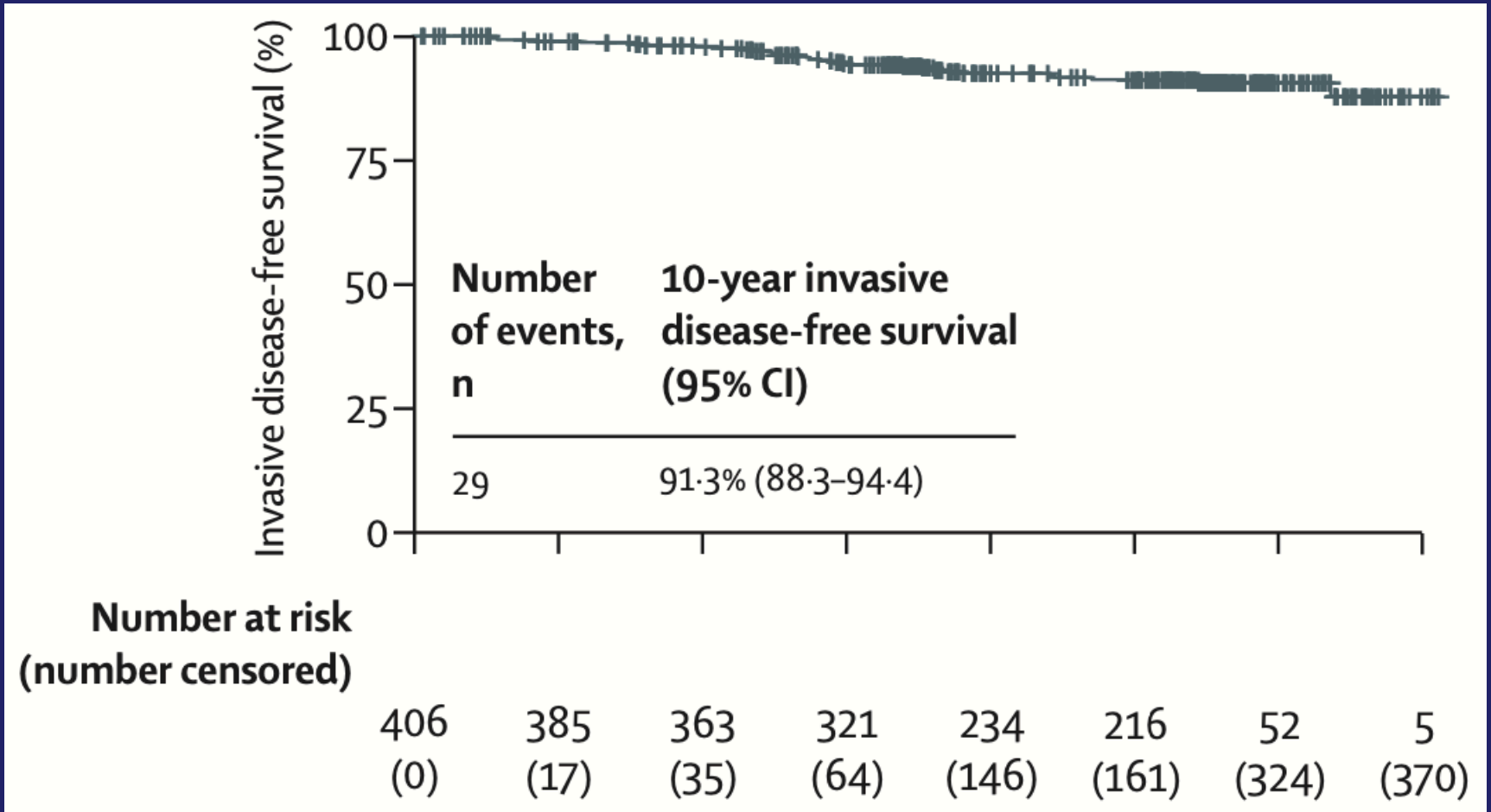
Receipt of chemo was not randomized thus confounding variables may bias results, affecting the observed differences

Johnson K, et al. *Npj Breast Cancer*. 2024;10:49

10-year Analysis of Phase II Trial of Adjuvant Paclitaxel (weekly x 12) and Trastuzumab (1-year) (APT) for Node-Neg, HER2+

Note:
2/3 HR+; 19% T1a, 31% T1b; 42% T1c

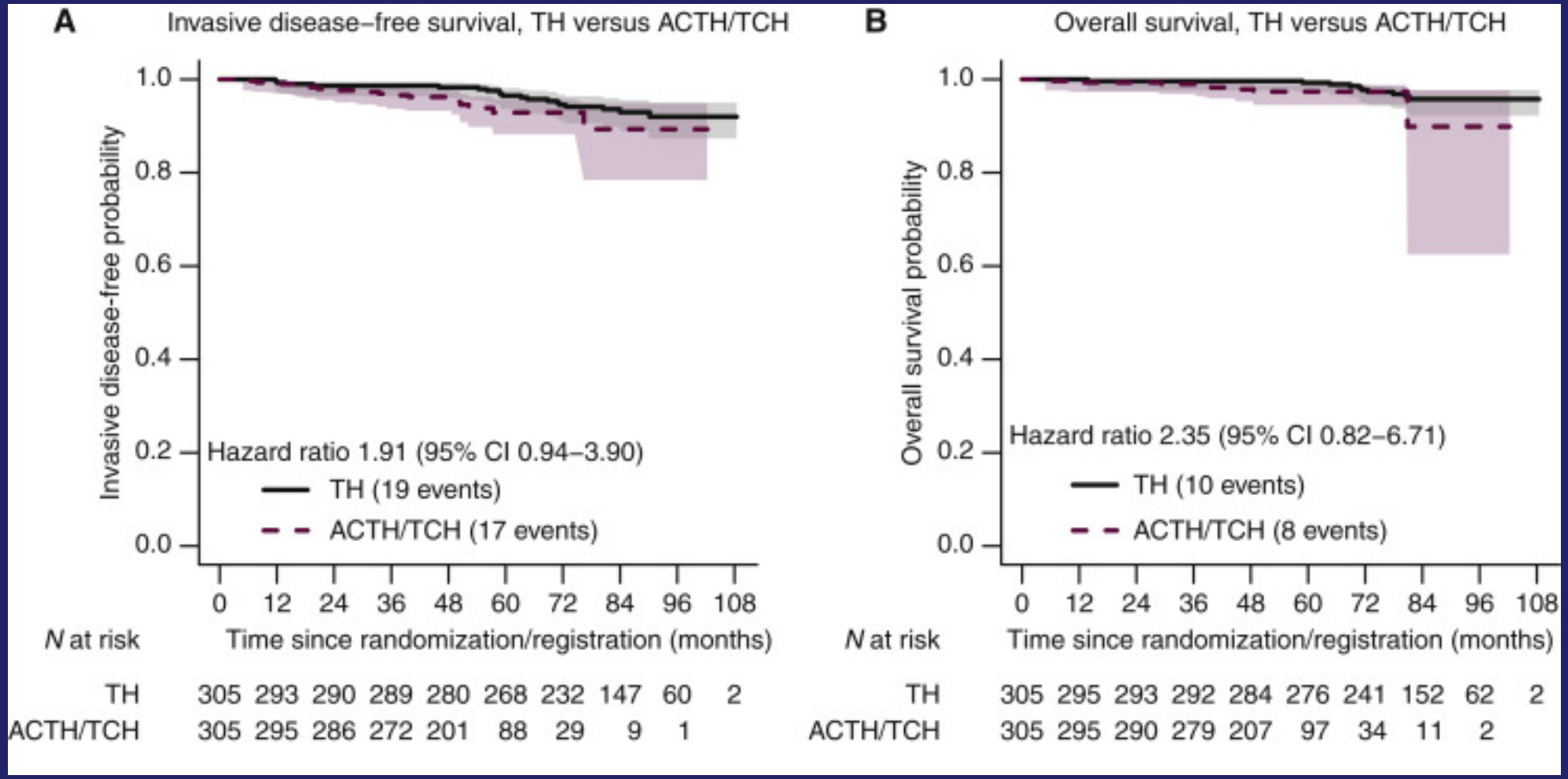
10-year RFI (excludes death from non-BC/contralateral BC) 96.3%



Tolaney SM, et al. *Lancet Oncol*. 2023 Mar;24(3):273-285.

FDA Analysis of 5 RCTs

Propensity Score Matching to Compare iDFS of APT with ACTH/TCH in T≤3.0 Node Negative BC



Amiri-Kordestani L, et al. *Ann Oncol.* 2020;31:1704-08

How Do I Treat Small node negative (cT1a/T1b) HER2+?

Weekly paclitaxel x 12 plus trastuzumab x 1 year

How Do I Treat ≥cT1c or Clinically Node Positive Tumors?

Neoadjuvant Setting is Not Just a Research Tool

Acting on residual disease has long term impact in HER2+ BC

KATHERINE TRIAL (8.4 years follow uP)

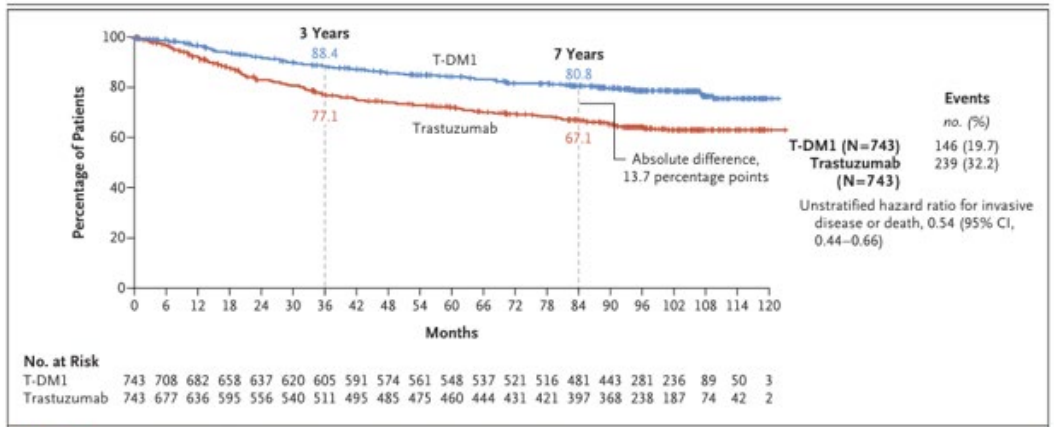


Figure 1. Invasive Disease–free Survival in the Intention-to-Treat Population.
Invasive disease–free survival was defined as the time from randomization until the first occurrence of one of the following events: ipsilateral invasive disease, ipsilateral locoregional invasive disease, contralateral invasive breast cancer, distant recurrence, or death from any cause. T-DM1 denotes trastuzumab emtansine.

Neoadjuvant treatment also reduces amount of surgery (mastectomy, axillary lymph node dissection)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival with Trastuzumab Emtansine in Residual HER2-Positive Breast Cancer

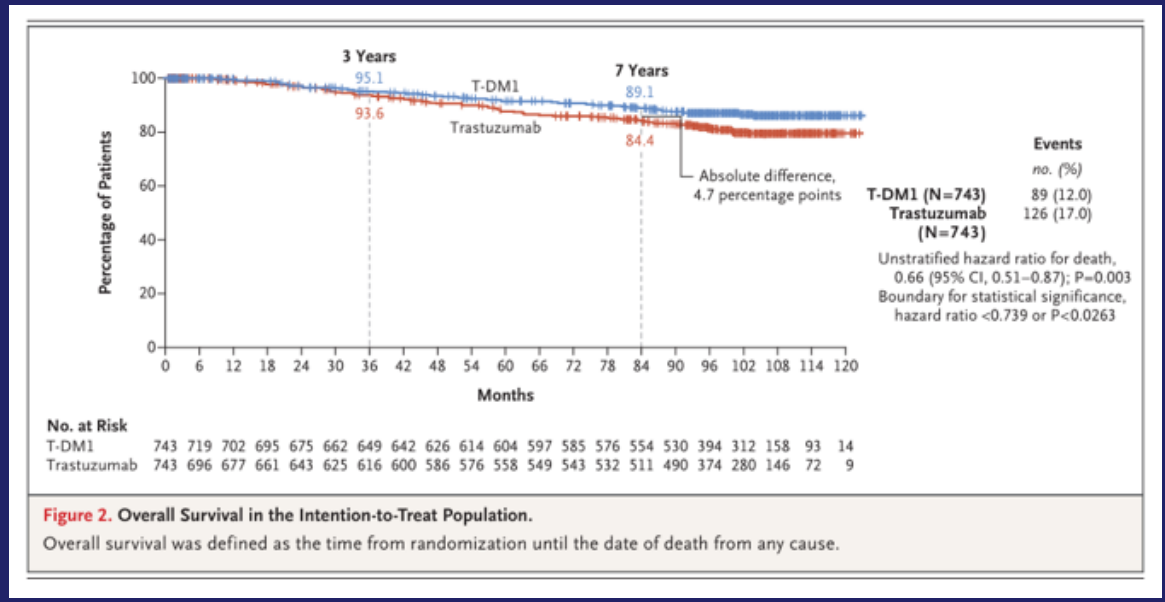


Figure 2. Overall Survival in the Intention-to-Treat Population.
Overall survival was defined as the time from randomization until the date of death from any cause.

Geyer C et al. 2025;392:249-57.

For a patient with clinical node negative disease that is T1, should I offer neoadjuvant therapy or upfront surgery?

What is the risk that the patient has occult node positive disease?

Nodal Status in HER2+ cN0 Disease Treated with Upfront Surgery: Two International Cohorts

	Upfront Surgery Patients N= 368	
	Pathologic Node Positive	
Center	USA N=368	Spain N=119
cT Category		
Total	73/368 (19.8%)	25/119 (21%)
1mic	6/48 (10.4%)	0/2
1a	3/26 (11.5%)	1/8 (12.5%)
1b	7/87 (8.0%)	3/34 (8.8%)
1c	38/154 (24.7%)	16/56 (28.6%)

- 20% of patients with clinical node negative disease had node positive disease at surgery
- 26% of patients with cT1cN0 tumors had pN+ disease at surgery
- 10% of pts with T1mi/a/b had pN+ disease

Weiss A et al. *Cancer* 2023;129:1836

Nodal Status in HER2+ cN0 Disease Treated with Upfront Surgery: Two International Cohorts

	Upfront Surgery Patients		Neoadjuvant Tx	
	Pathologic Node Positive		Pathologic Node Positive	
Center	USA N=368	Spain N=119	USA N=211	Spain N=173
cT Category Total	73/368 (19.8%)	25/119 (21%)	26/211 (12.3%)	18/173 (10.4%)
1mic	6/48 (10.4%)	0/2	-	-
1a	3/26 (11.5%)	1/8 (12.5%)	-	-
1b	7/87 (8.0%)	3/34 (8.8%)	1/7 (14.3%)	0/4
1c	38/154 (24.7%)	16/56 (28.6%)	5/30 (16.7%)	9/68 (13.2%)

Weiss A et al. *Cancer* 2023;129:1836

How Do I Treat ≥cT1c or Clinically Node Positive Tumors

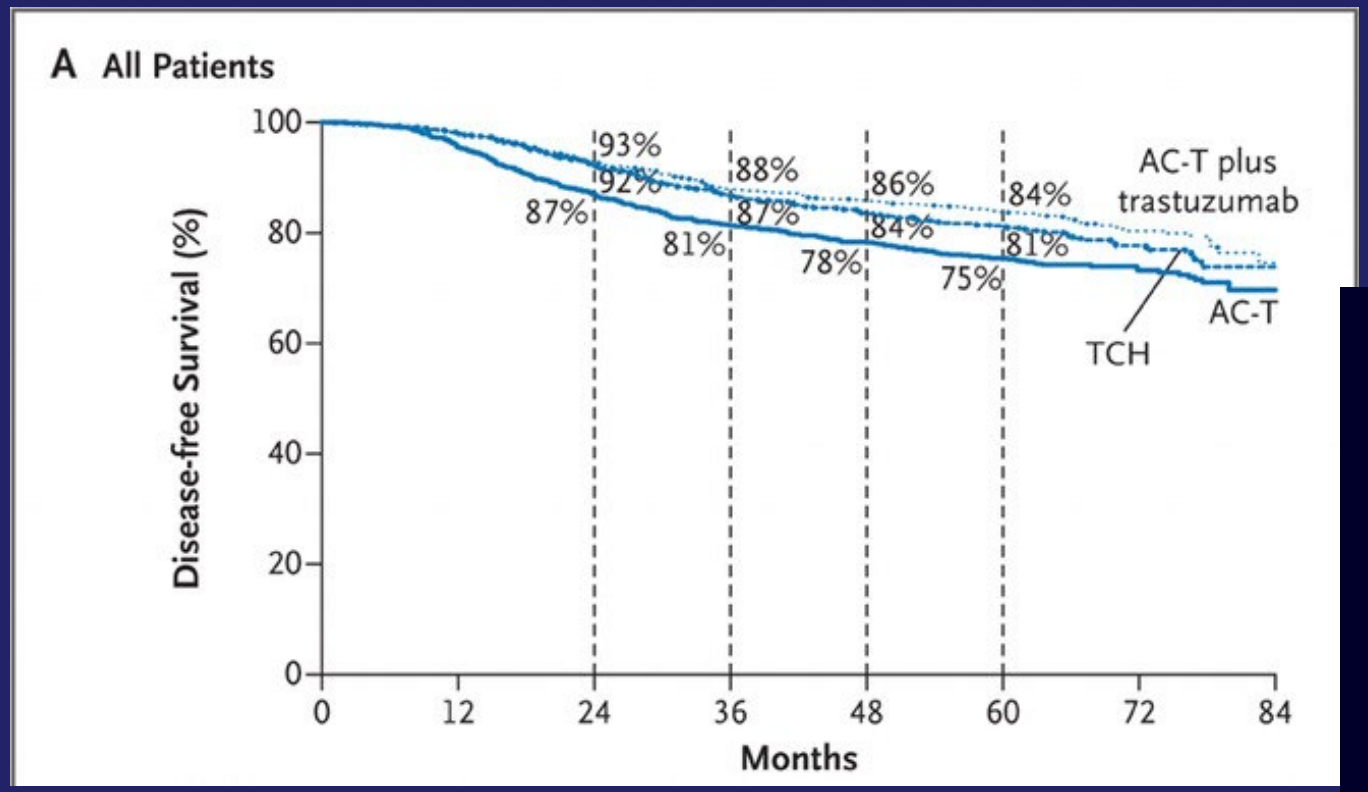
Neoadjuvant Therapy

What systemic therapy should I use for LN+ or T1c+ Disease?

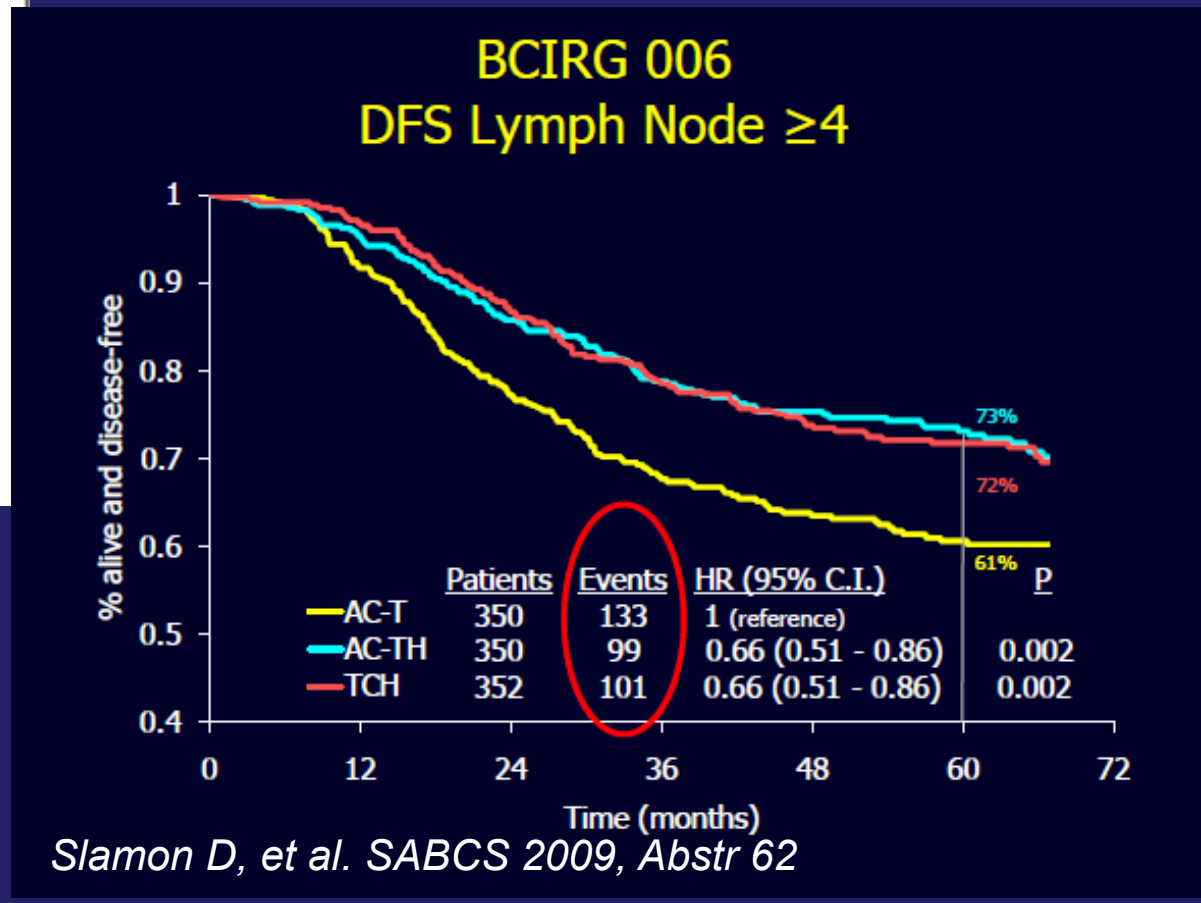
Anthracyclines?

Platinum vs No-platinum?

BCIRG006: TCH vs AC-TH Regimen



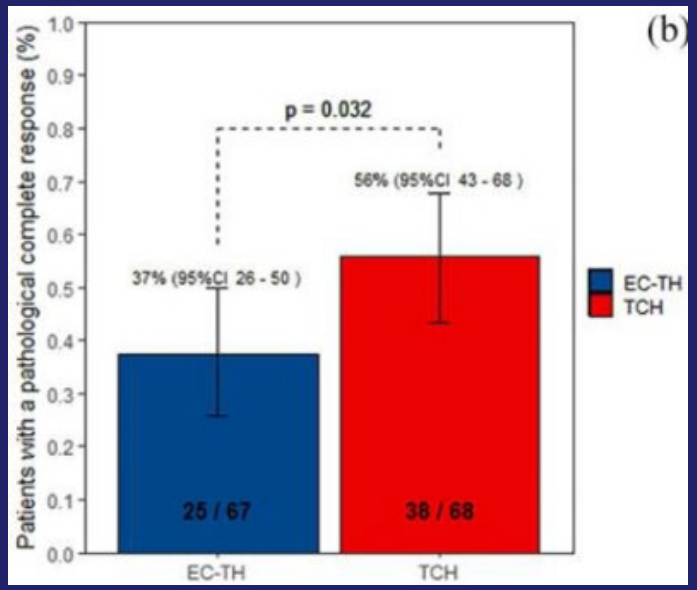
Slamon D et al. N Engl J Med 2011;365:1273-1283.



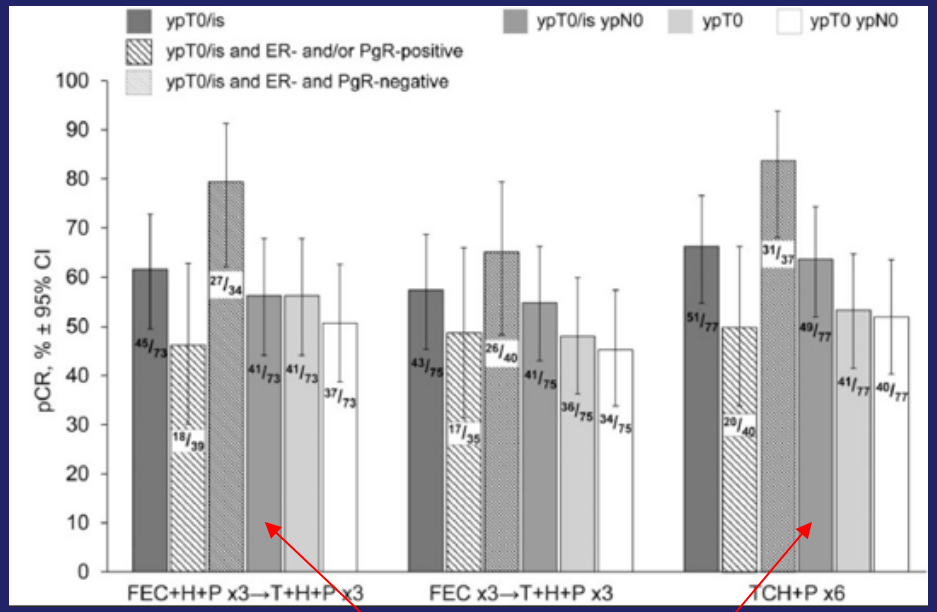
Slamon D, et al. SABCS 2009, Abstr 62

Neoadjuvant Trials of Anthracycline vs Non-Anthracycline Based Regimens in HER2+ BC

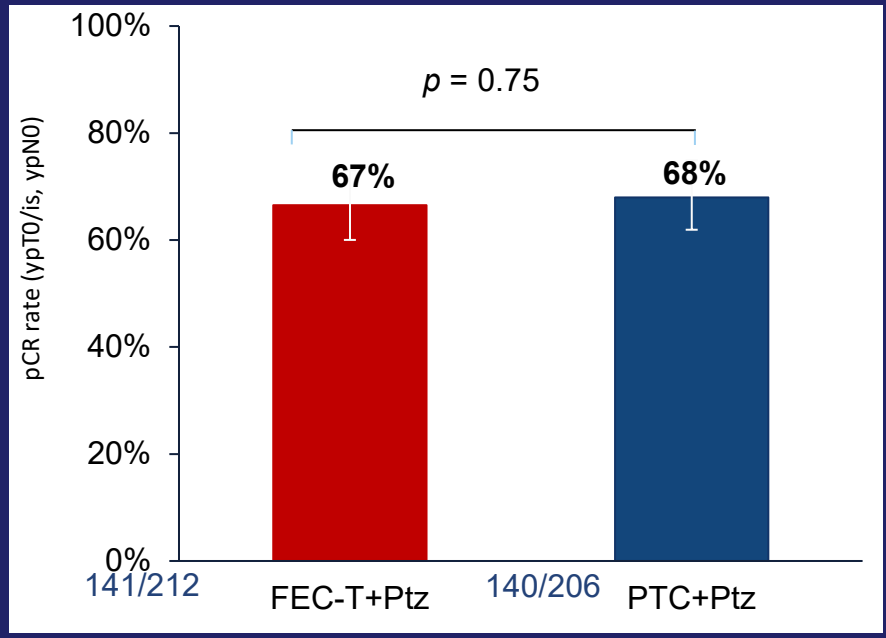
NeoCARH



TRYPHAENA



TRAIN-2

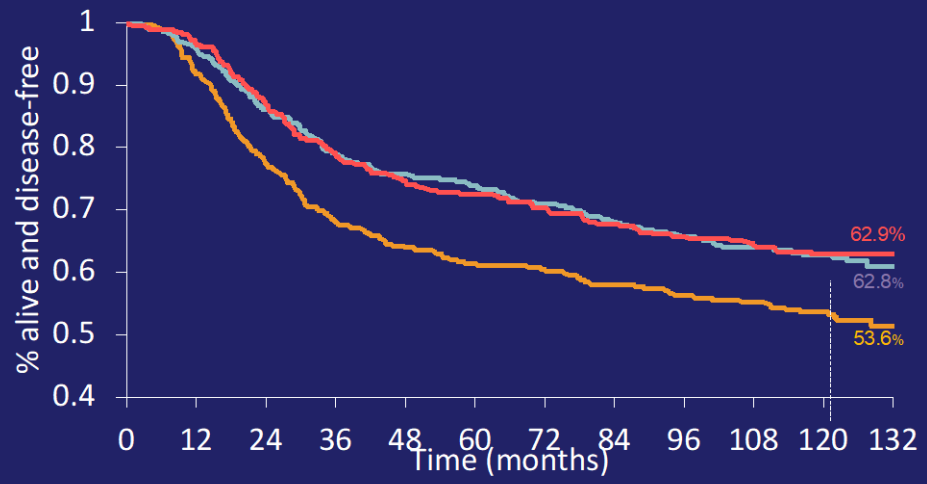


ypT0/is ypN0
FECHP-THP < TCHP

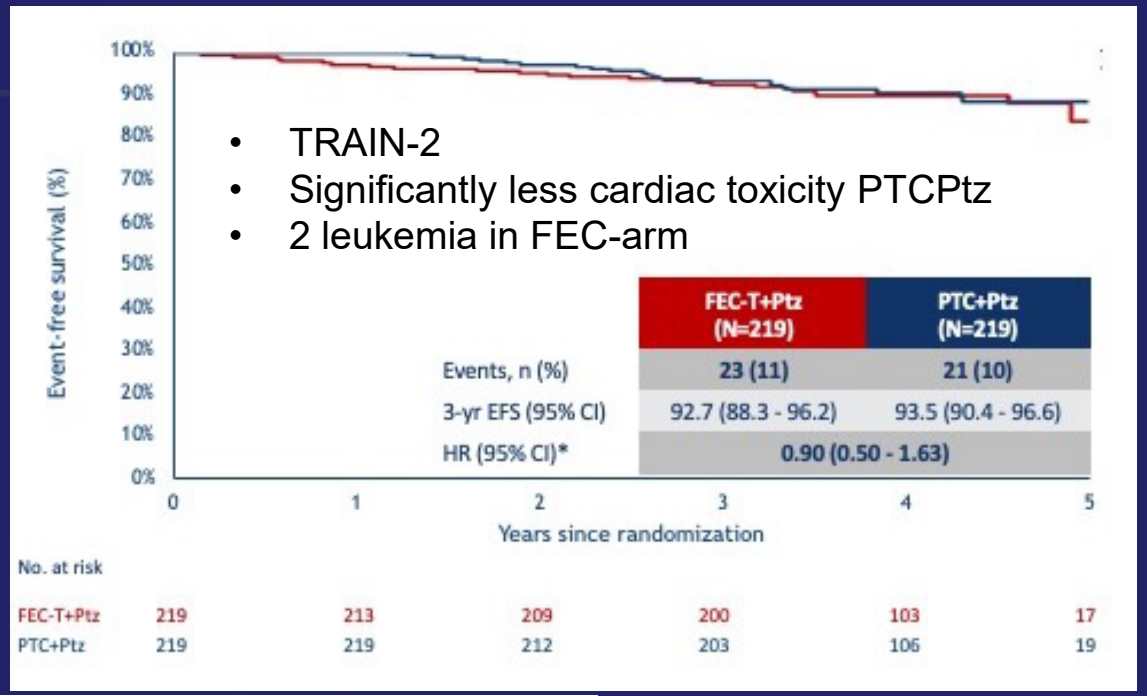
Gao HF, et al. Ther Adv Med Oncol. 2021;13; Schneeweiss A, et al. Ann Oncol. 2013;24:2278-84; van Ramshorst et al, *Lancet Oncol* 2018;19

Disease Free/Event Free Survival Anthracycline vs. Non-Anthracycline Based Regimens for HER2+

BCIRG 006 DFS Lymph Node ≥4

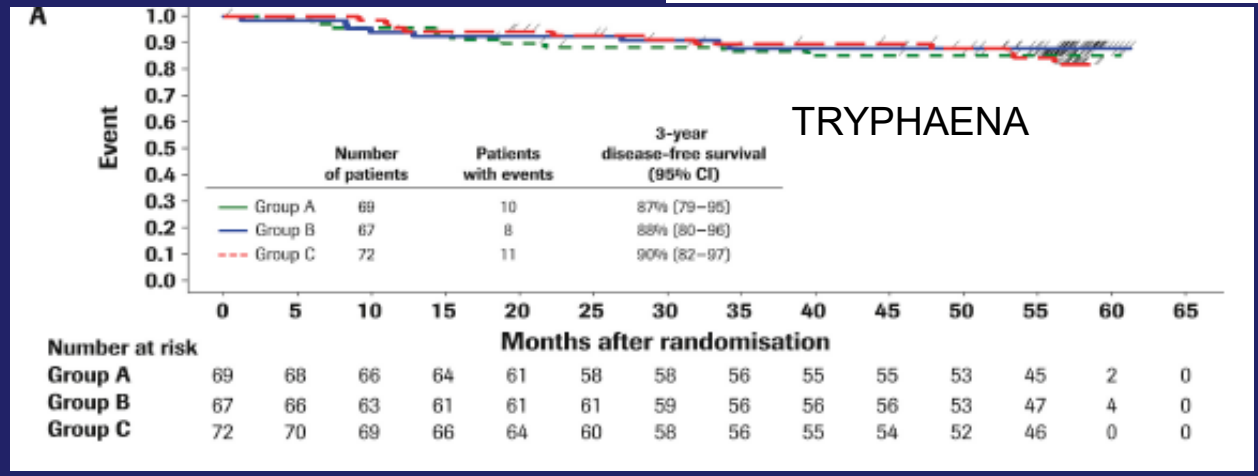


Slamon D et al. Ca Research 2015;76: Abstr S5-04



- TRAIN-2
- Significantly less cardiac toxicity PTCPtz
- 2 leukemia in FEC-arm

Van der Voort A, et al. JAMA Oncol. 2021;7:978-84.



TRYPHAENA

Schneeweiss A, et al. Eur J Cancer 2018;89:27-35.

Cardiomyopathy in HER2+ Disease

- Rate of CHF or cardiac death in trastuzumab-treated patients at 6-7 years up to 4.0%
- Proportion who could not receive trastuzumab after AC due to cardiomyopathy, up to 7%
- **Occult heart damage difficult to gauge; studies only measured LVEF in asymptomatic pts 18-21 mos**
  - B31: 15.5% (N=147) in total stopped trastuzumab early due to cardiac related issues
  - N9831: Up to 24% in ACTH arm had LVEF drop below normal

Romond et al. JCO 2012;30:3792-99
Advani et al. JCO 2016;34:581-88

What systemic therapy should I use for LN+ or T1c+ Disease?

Anthracycline Free, Taxane Based Neoadjuvant Therapy

pCR for Neoadjuvant Taxane/Carbo-Based HER2-Targeted Therapy

Regimen/ Study		pCR
TCH x 6 **TRIO B07/Hurvitz SA, et al. Nat Commun. 2020;11:5824**	34	**47%**
TCH x 6 **neoCARH/Gao HF, et al. Ther Adv Med Oncol. 2021**	68	**56%**
TCHP x 6 **TRYPHAENA/Schneeweiss, et al. An**	75	**64%**
TCHP x 6 KRISTINE-TRIO-02 [illegible] al. Lancet Oncol 2018	221	**56%**
TCHP x 4 (in[illegible] **NSABP B[illegible], et al. Cancer Res 2016, SABCS S3-06**	155	***41%*** ***HR+ only***
Paclitaxel/Carbo/Trastuzumab/Pertuzumab x 9 **TRAIN-2/van Ramshorst et al. Lancet Oncol 2018**	206	**68%**
TCHP x 6 **PHERGAIN/Perez-Garcia, et al. Lancet 2021**	71	**58%**

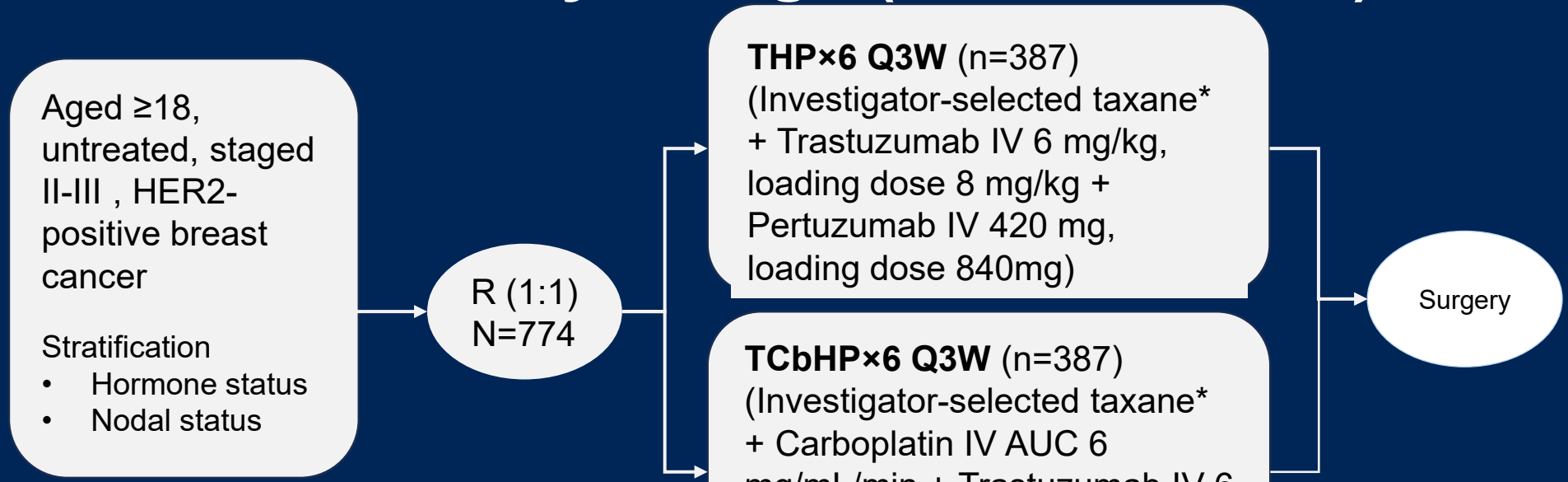
Can we omit carboplatin??

Select Neoadjuvant Non-Anthracycline Taxane + HP Regimens

Regimen/ Study	N	pCR
Docetaxel + Trastuzumab/Pertuzumab (HP) x 4 cycles **NeoSphere**	107	**39.3%**
Docetaxel + HP x 6 cycles **PREDIX HER2**	99	**45.5%**
Paclitaxel x 12 weeks + HP **WSG-ADAPT-HR-/HER2+**	42	**90.5%**
Paclitaxel x 12 weeks + HP Triple Positive-II (TPII)	107	**56.9%**
Paclitaxel x 12 weeks + HP **DAPHNE**	98	**57%**

1. NeoSphere: Gianni L, et al. *Lancet Oncol*. 2012;13:25-32; Gianni L, et al. *Lancet Oncol*. 2016;17:791–800. 2. ADAPT HR-: Nitz U, etl a. *Annals Oncol*. 2017. 3; 3. Triple Positive-II: Gluz O, et al. *JAMA Oncol*. 2023; 4. PREDIX HER2: Hatschek T, et al. *JAMA Oncol*. 2021;7:1360-1367. 5. DAPHNE: Waks AG, et al. npj Breast Cancer 2022.

neoCARHP Study Design (NCT04858529)



- Primary endpoint: pCR (ypT0/is ypN0)
- Secondary endpoints: Safety, clinical response during neoadjuvant therapy, the percentage of patients who underwent breast-conserving surgery, EFS, DFS, OS

* Docetaxel, Paclitaxel or Nab-paclitaxel

***Potential Limitation*: All taxane given q3 weeks. Studies have indicated that for paclitaxel and nab-paclitaxel, weekly dosing may be superior**

Green MC. J Clin Oncol 2005;23. Sparano J. NEJM 2008;358:1663-71. Seidman A. J Clin Oncol. 2008;26:1642–9. Martin M. Breast Cancer Res 2015;17.

Baseline Patients Characteristics

	THP (n=382)	TCbHP (n=384)
Age (median [IQR], years)	52 (45-58)	51 (44-56)
Menopausal status, n (%)		
Premenopausal	191 (50.0%)	200 (52.1%)
Postmenopausal	191 (50.0%)	184 (47.9%)
T stage, n (%)		
T1-2	311 (81.4%)	302 (78.6%)
T3-4	71 (18.6%)	82 (21.4%)
Nodal status, n (%)		
Negative	137 (35.9%)	138 (35.9%)
Positive	245 (64.1%)	246 (64.1%)
Disease stage, n (%)		
Stage II	294 (77.0%)	275 (71.6%)
Stage III	88 (23.0%)	109 (28.4%)
Histological type, n (%)		
Ductal	375 (98.2%)	376 (97.9%)
Lobular	1 (0.3%)	2 (0.5%)
Others	6 (1.6%)	6 (1.6%)

	THP (n=382)	TCbHP (n=384)
Hormone receptor status, n (%)		
ER-negative andPR-negative	142 (37.2%)	144 (37.5%)
ER-positive and/orPR-positive	240 (62.8%)	240 (62.5%)
HER2 status, n (%)		
Immunohistochemistry 3+	338 (88.5%)	348 (90.6%)
Immunohistochemistry 2+ and ISH-positive	44 (11.5%)	36 (9.4%)
Ki67, n (%)		
≤30%	163 (42.7%)	172 (44.8%)
>30%	219 (57.3%)	212 (55.2%)
Taxane therapy, n (%)		
Nab-paclitaxel* Q3 wk	170 (44.5%)	171 (44.5%)
Docetaxel	137 (35.9%)	141 (36.7%)
Paclitaxel Q3 wk	75 (19.6%)	72 (18.8%)

*nab-paclitaxel not FDA approved for this indication

Pathologic Complete Response
No different by adding carboplatin

Trial	pCR Overall	pCR in ER-positive	pCR in ER-negative
neoCARHP-TCHPx6	66%	59%	78%
neoCARHP-THPx6	64%	56%	78%

Safety:

- Increased grade 3/4 adverse events in TCHP arm: neutropenia (16.4% vs 6.8%), febrile neutropenia (2.6% vs. 1.3%), thrombocytopenia (4.2% vs. 0.3%), anemia (6.6% vs. 2.1%)

- Higher all grade nausea, vomiting, increased creatinine

HELEN-006 Phase 3 RCT:

Population Enrolled:

64% stage II

36% stage III

73% node-positive

Stage II-III
HER2+ BC
Age 18-70 yo

N=669

1:1

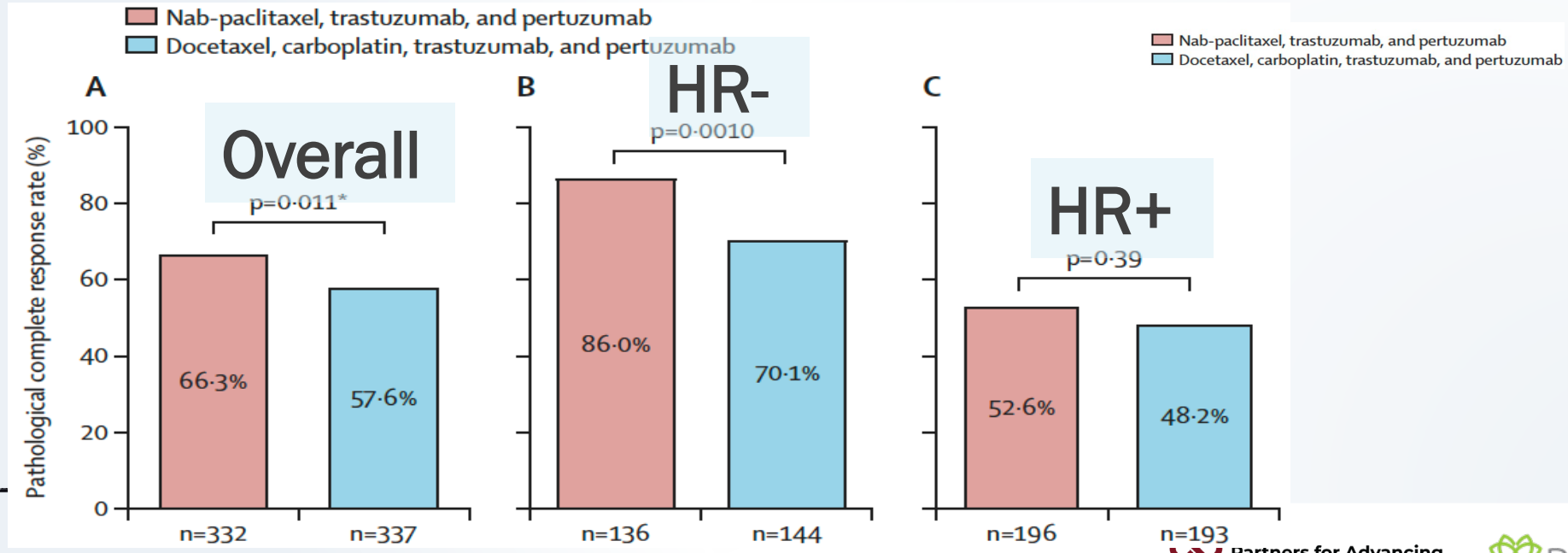
Docetaxel/carbo/HP
x18 weeks

Weekly nab-paclitaxel/HP
x18 weeks

Primary Endpoint: pCR (ypT0/is N0)

Superiority design

(hypothesis: nab-paclitaxel > docetaxel arm)



Chen X-C et al. *Lancet Oncol*. 2025;26(1):27-36.

Atlanta Breast Cancer CONFERENCE

Partners for Advancing Clinical Education

Bio Ascend™

Pathology Complete Response across trials

		Overall	HR-	HR+
Taxane-HP x12 wks	Tax-HP (CompassHER2-pCR)	44%	64%	33%
	THP (DAPHNe)	57%	85%	42%
	THP (WSG-TP-II)	-	-	56%
	DHP (NeoSphere)	45%	-	-
Taxane-HP x18 wks	nab-THP (HELEN006)	66%	86%	53%
	Tax-HP (NeoCARHP)	64%	78%	56%
Taxane-Cb-HP x18 wks	DCbHP (TRYPHAENA)	52%	-	-
	DCbHP (KRISTINE)	56%	73%	44%
	DCbHP (HELEN006)	58%	70%	48%
	Tax-CbHP (NeoCARHP)	66%	78%	59%

Cb: carboplatin; D: docetaxel; T: paclitaxel; Tax: mix of taxanes

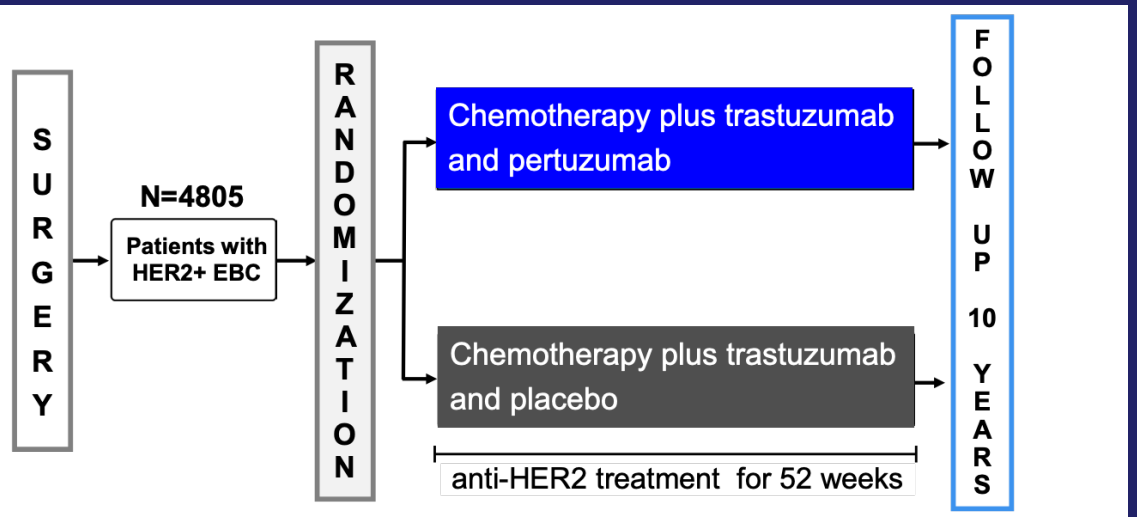
Waks AG et al *Nat Rev Clin Oncol* 2025. Gao H-F et al. ASCO 2025. Chen X-C et al. *Lancet Oncol*. 2025.

When Do I Omit Carboplatin?

Stage II Disease, will consider omission

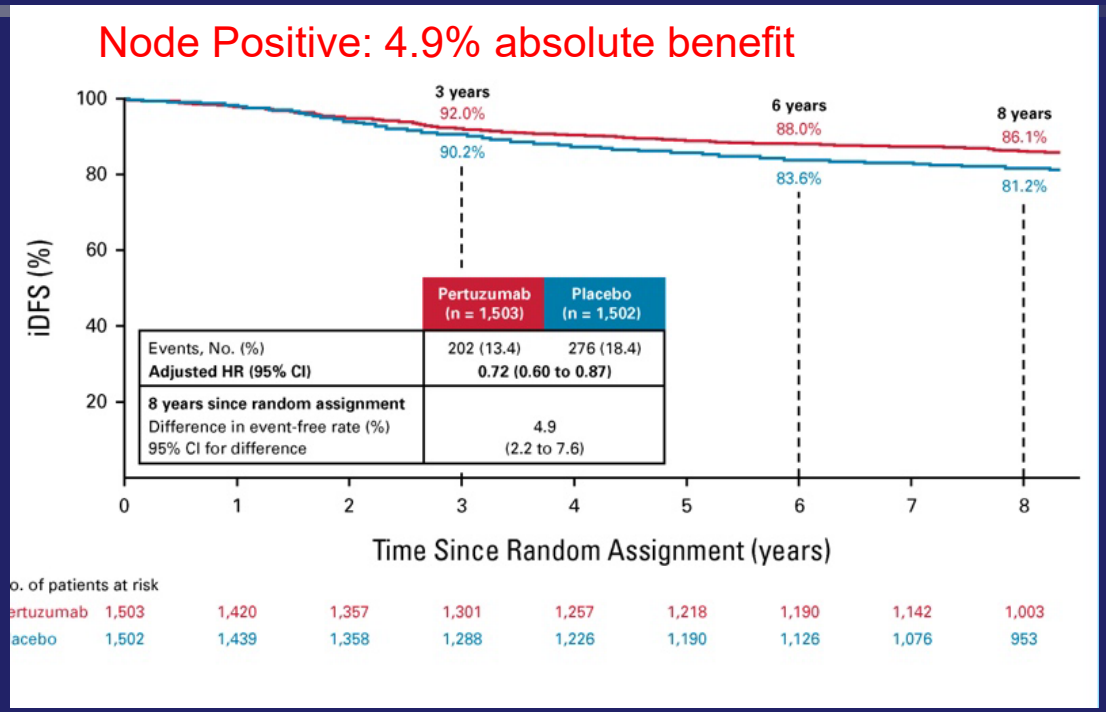
How Do I Treat Very High Risk Disease (Node Positive, Residual Disease)

APHINITY: Adjuvant Pertuzumab 8-year iDFS



Primary endpoint: iDFS

- Large Global trial: US highest enrolling country
- Anthracycline or non-anthracycline based chemo allowed
- IDMC and Independent Cardiac Review Committee



No differential benefit based on HR status

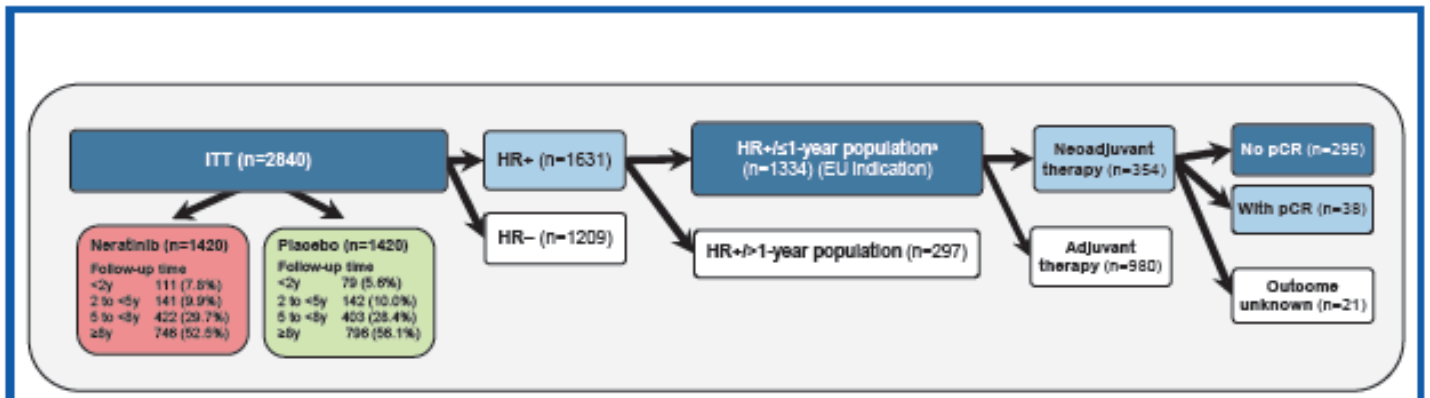
New Data 2025: OS difference in the ITT population with 11.3 yrs median f/u

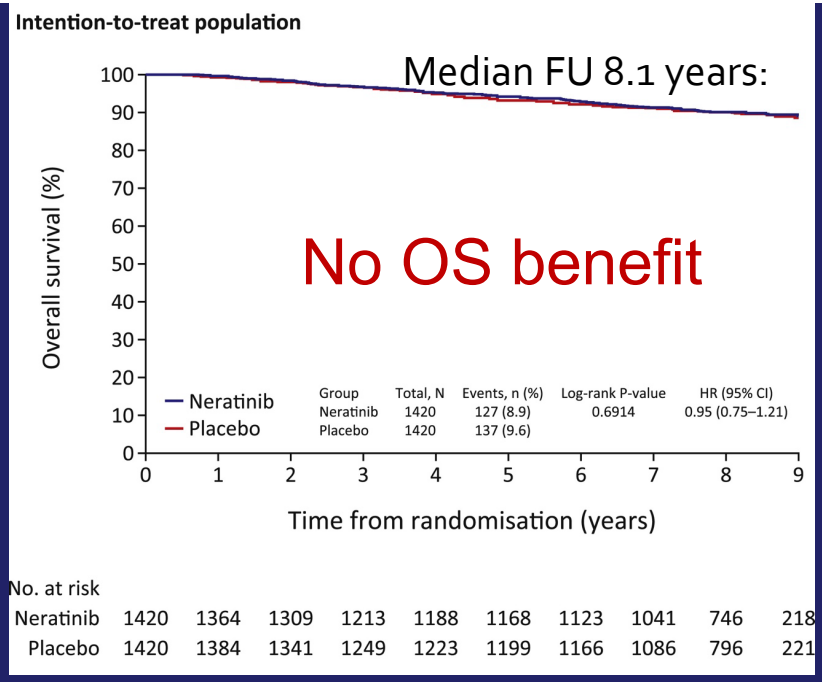
- HR 0.83 (△1.8%) in ITT
- HR 0.79 (△2.7%) in node-positive
- Loibl S et al. *ESMO Breast*. 2025.

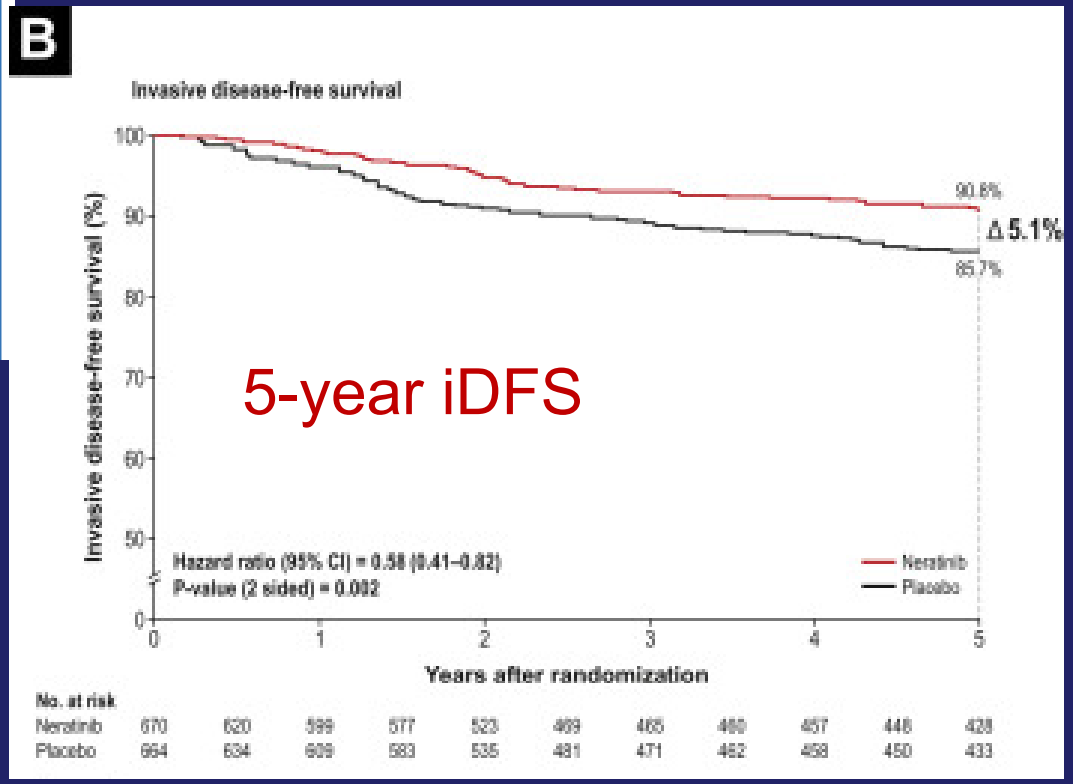
Loibl S et al. J Clin Oncol. 2024;42

Extended Adjuvant HER2-Targeted Therapy

ExteNET: Neratinib







*Benefit restricted to Hormone Receptor Positive

Martin M et al. Lancet Oncol. 2017;18:1688. Chan A et al. Clin Breast Ca. 2021;21:p80. Holmes F et al. European J Cancer. 2023;184:48

KEY TAKEAWAY:
Current Strategy for HER2-Positive Stage I-III

cT1a/b cN0

Surgery followed by trastuzumab-based therapy *alone (T1a) or with chemo or endocrine therapy*

≥cT1c or ≥cN1

Neoadjuvant TCHP

Think carefully about who really needs anthracycline. Data does not indicate that benefit is gained.

Residual invasive disease

tpCR (ypT0/is ypN0)

T-DM1 x 14

Neratinib if HR+ and LN+*

H x 1 yr

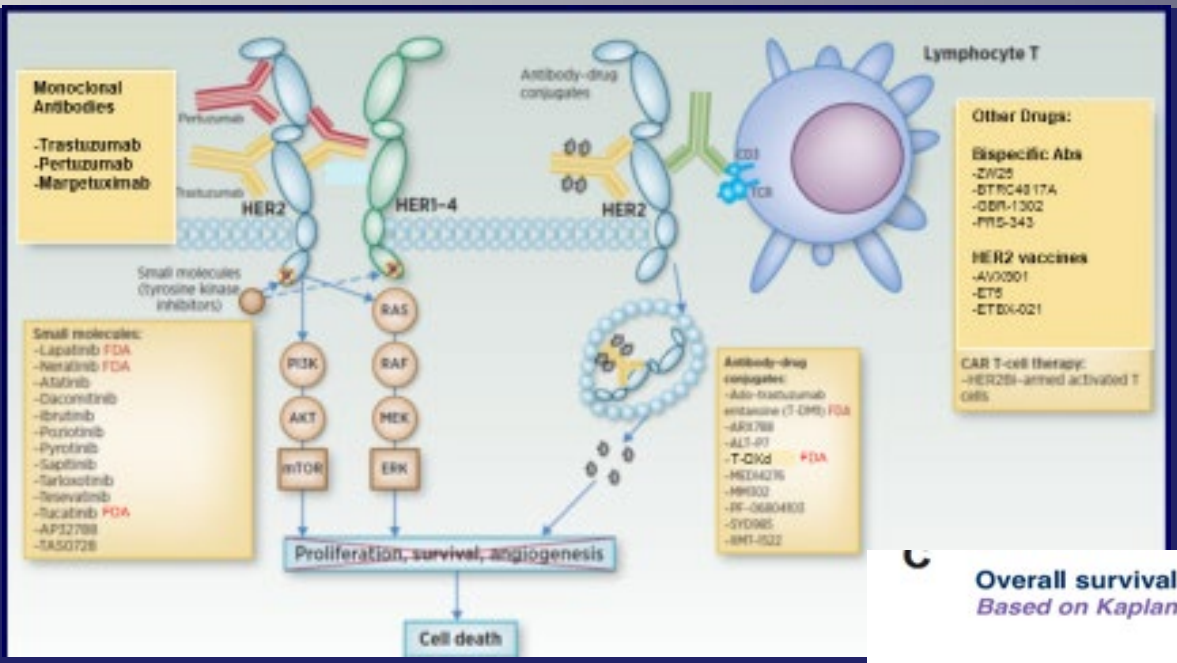
HP x 1 yr if started LN+ *; Consider neratinib for very high risk HR+ even if pCR (CNS protection)****

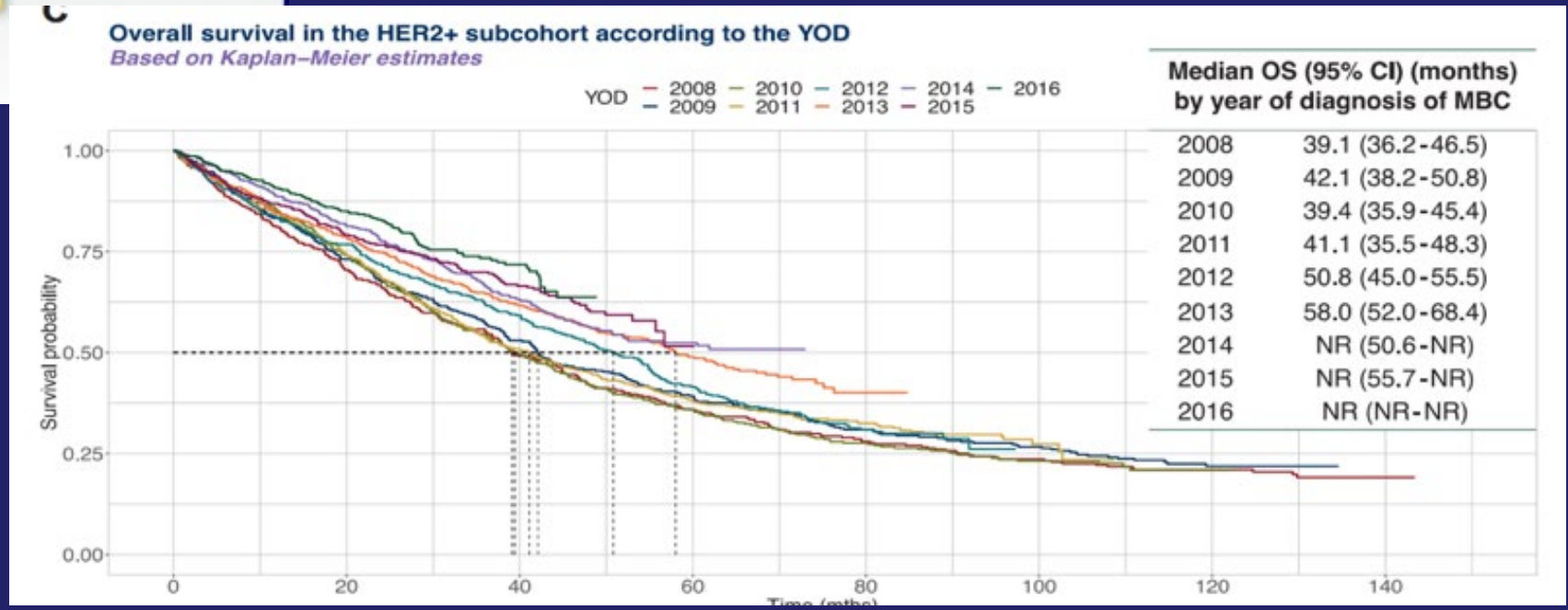
**neratinib not tested after T-DM1 or pertuzumab in EXTENET

***adjuvant pertuzumab not tested after neoadjuvant pertuzumab in APHIINTY

How Do I Treat Stage IV Disease?

An Expanding Armementarium Is Improving Outcomes for HER2+ Disease

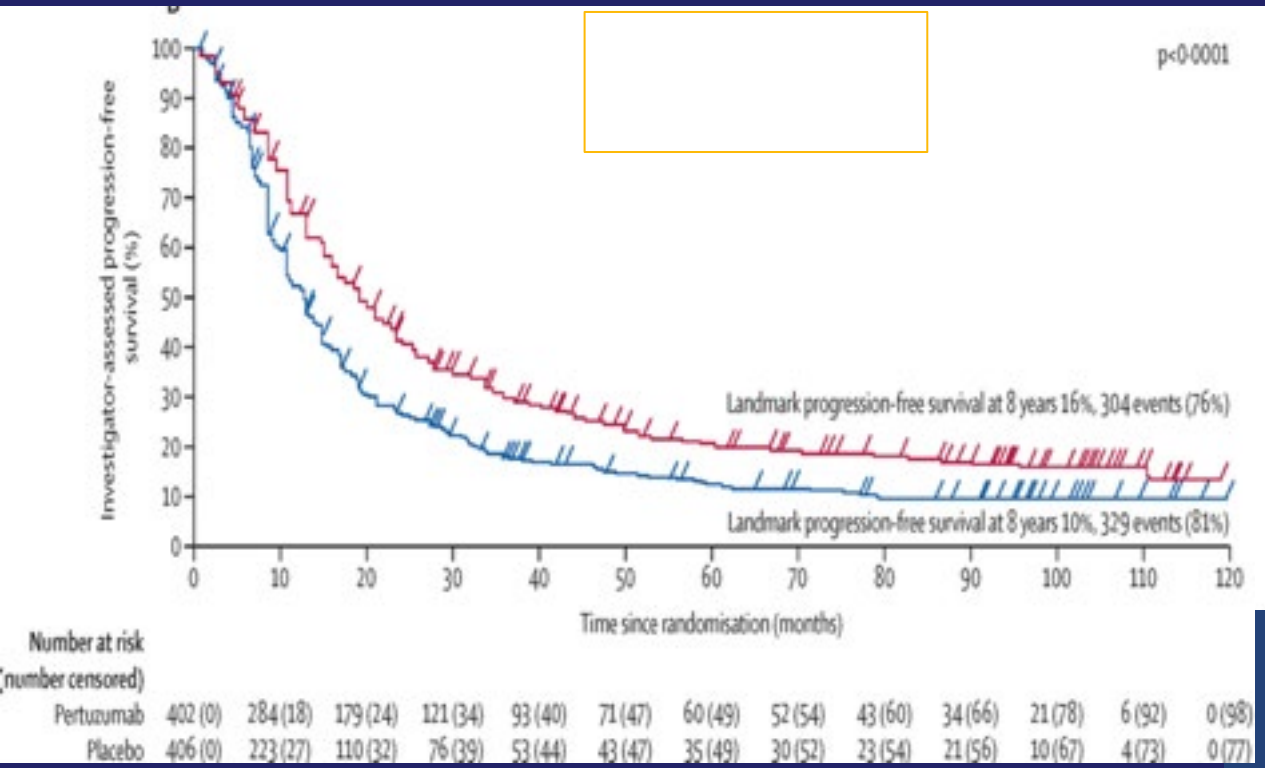


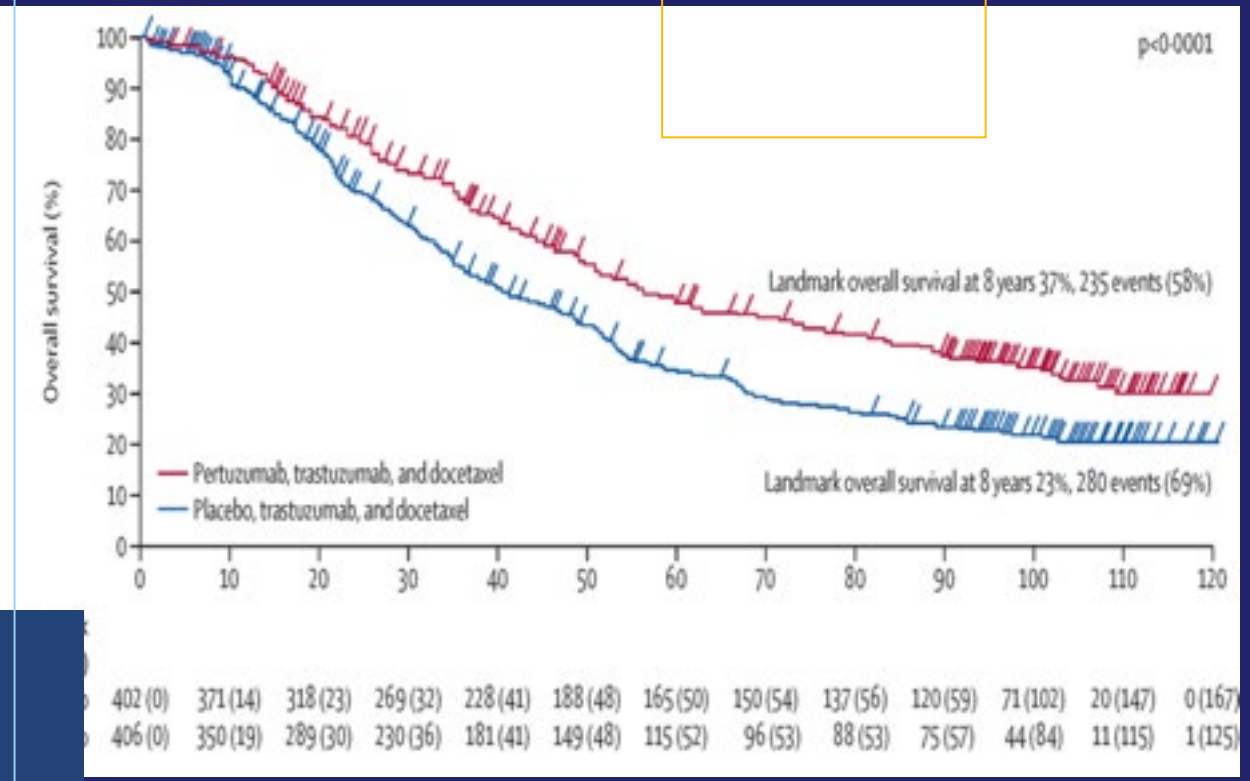


Bernstam FM, Clin Cancer Res 2019;25:2033
Grinda T, et al. ESMO Open. 2021;6:100114.

CLEOPATRA End-of-Study Results:
Adding Pertuzumab to Taxane + Trastuzumab Improves PFS and OS

(median follow-up ~100 months)



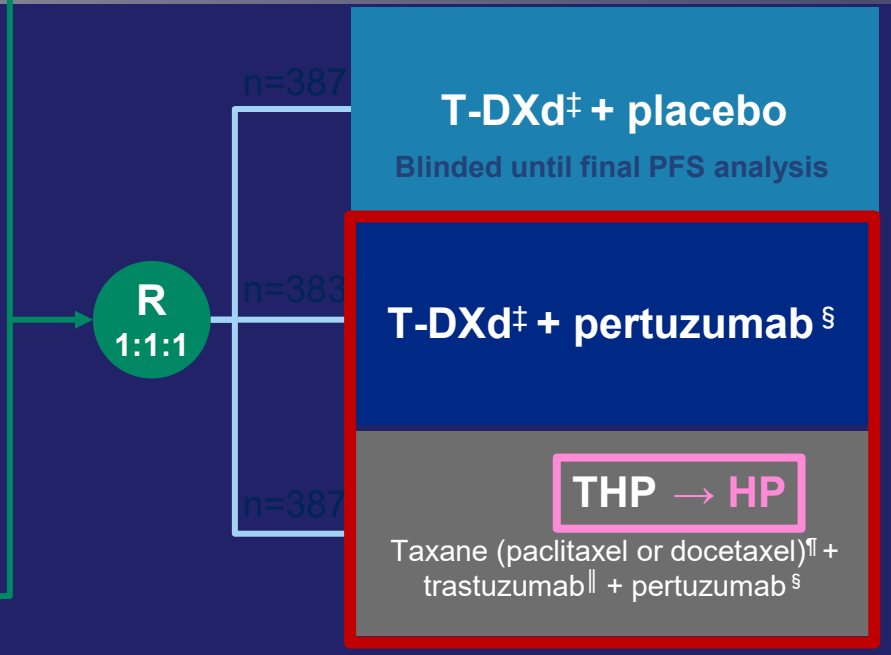


Swain S, et al. Lancet Oncol. 2020;21:519-530.

DESTINY-Breast09 – 1L HER2+ mBC

Eligibility criteria

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



Endpoints

Primary

- PFS (BICR)

Key secondary

- OS

Secondary

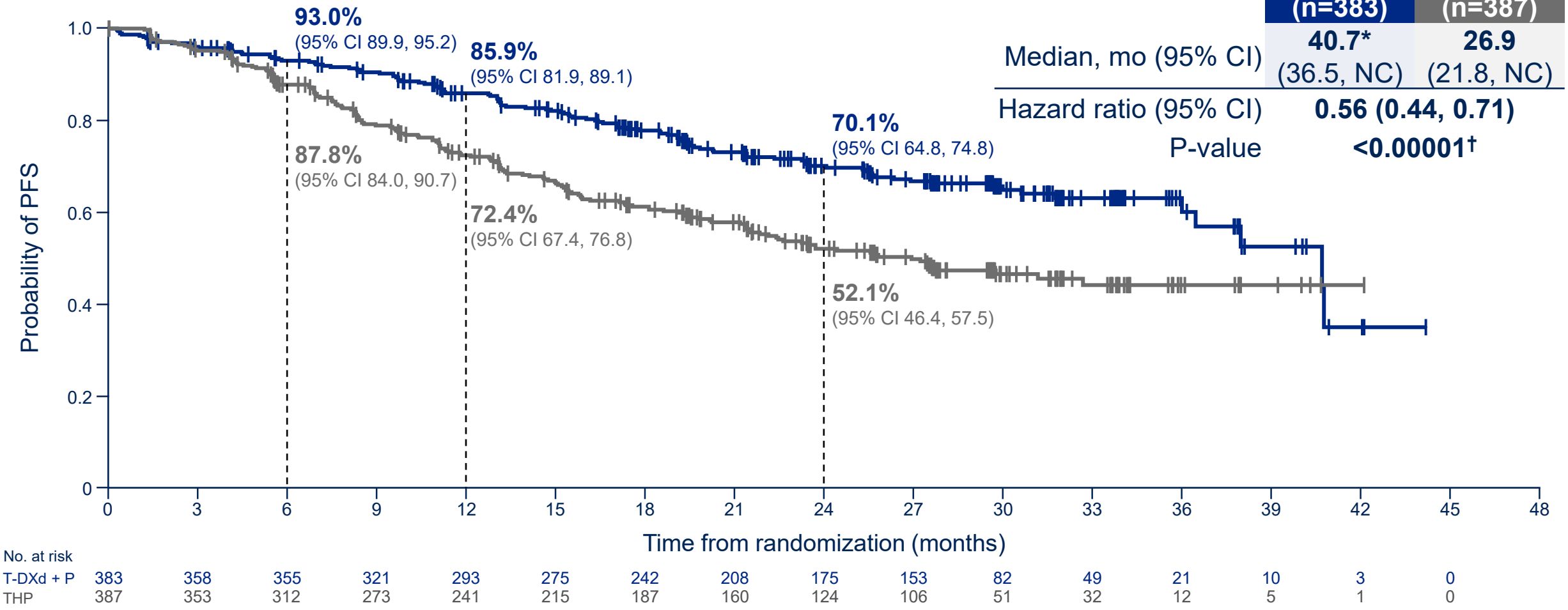
- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerability

- **<u>Key participant characteristics</u>:**
  - 51% de novo mBC; 54% HR+; ~82% IHC 3+
  - Of those initially diagnosed with ESB: ~ 80-85% received (neo)adjuvant chemo; **~ 58% trastuzumab**; **~15% pertuzumab**; **2% T-DM1**
  - Concurrent use of **ET in HR+**: **13.5% in T-DXd + P arm**; **38.3% in THP arm**

Tolaney S et al ASCO 2025

DB09 PFS (BICR): primary endpoint

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



No. at risk

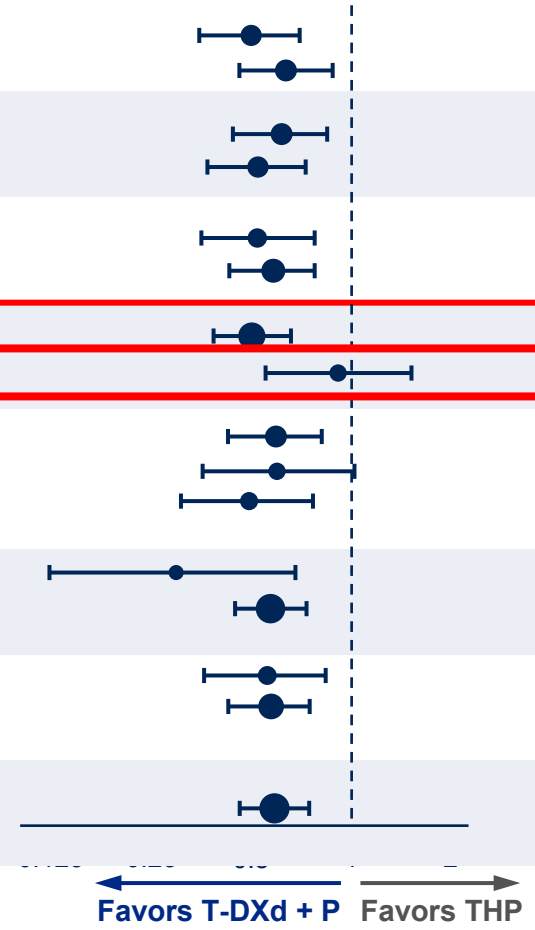
T-DXd + P	383	358	355	321	293	275	242	208	175	153	82	49	21	10	3	0
THP	387	353	312	273	241	215	187	160	124	106	51	32	12	5	1	0

Statistically significant and clinically meaningful PFS benefit with T-DXd + P (median Δ 13.8 mo)

*Median PFS estimate for T-DXd + P is likely to change at updated analysis; †stratified log-rank test. A P-value of <0.00043 was required for interim analysis superiority
BICR, blinded independent central review; CI, confidence interval; mo, months; (m)PFS, (median) progression-free survival; NC, not calculable; P, pertuzumab; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

DB09-PFS (BICR): subgroup analyses

	No. of events / no. of patients		mPFS, months (95% CI)		Hazard ratio (95% CI)
	T-DXd + P	THP	T-DXd + P	THP	
Prior treatment status					
De novo	52/200	85/200	NC (36.5, NC)	31.2 (23.5, NC)	0.49 (0.35, 0.70)
Recurrent	66/183	87/187	38.0 (26.9, NC)	22.5 (18.1, NC)	0.63 (0.46, 0.87)
HR status					
Positive	65/207	87/209	38.0 (36.0, NC)	27.7 (22.4, NC)	0.61 (0.44, 0.84)
Negative	53/176	85/178	40.7 (40.7, NC)	22.6 (17.3, 32.7)	0.52 (0.37, 0.73)
***PIK3CA* mutation status**					
Detected	41/116	64/121	36.0 (29.7, NC)	18.1 (15.1, 25.6)	0.52 (0.35, 0.77)
Not detected	76/266	108/266	40.7 (38.0, NC)	32.7 (24.4, NC)	0.57 (0.43, 0.77)
Age at randomization					
<65 years	90/315	139/315	40.7 (36.5, NC)	27.4 (22.4, NC)	0.50 (0.38, 0.65)
≥65 years	28/68	33/72	27.6 (14.9, NC)	21.5 (13.9, NC)	0.92 (0.55, 1.51)
Geographical region					
Asia	62/188	87/191	40.7 (36.5, NC)	27.2 (21.5, NC)	0.60 (0.43, 0.83)
Western Europe and North America	27/87	31/78	36.0 (30.6, NC)	31.2 (15.8, NC)	0.60 (0.35, 1.01)
Rest of World	29/108	54/118	NC (38.0, NC)	24.4 (14.8, NC)	0.48 (0.30, 0.76)
Brain metastases at baseline					
Present	10/25	15/22	31.8 (18.5, NC)	9.5 (5.6, 13.3)	0.30 (0.12, 0.68)
Not present	108/358	157/365	40.7 (36.5, NC)	27.6 (22.6, NC)	0.58 (0.45, 0.74)
Prior exposure to anti-HER2 therapies					
Yes	39/115	51/112	38.0 (26.9, NC)	21.5 (15.3, NC)	0.55 (0.36, 0.83)
No	79/268	121/275	40.7 (36.5, NC)	27.6 (22.5, NC)	0.56 (0.42, 0.74)
Prior exposure to pertuzumab					
Yes	5/31	12/26	40.8 (25.4, NC)	19.8 (7.5, NC)	NC
No	113/352	160/361	40.7 (36.0, NC)	27.4 (22.4, NC)	0.61 (0.48, 0.77)

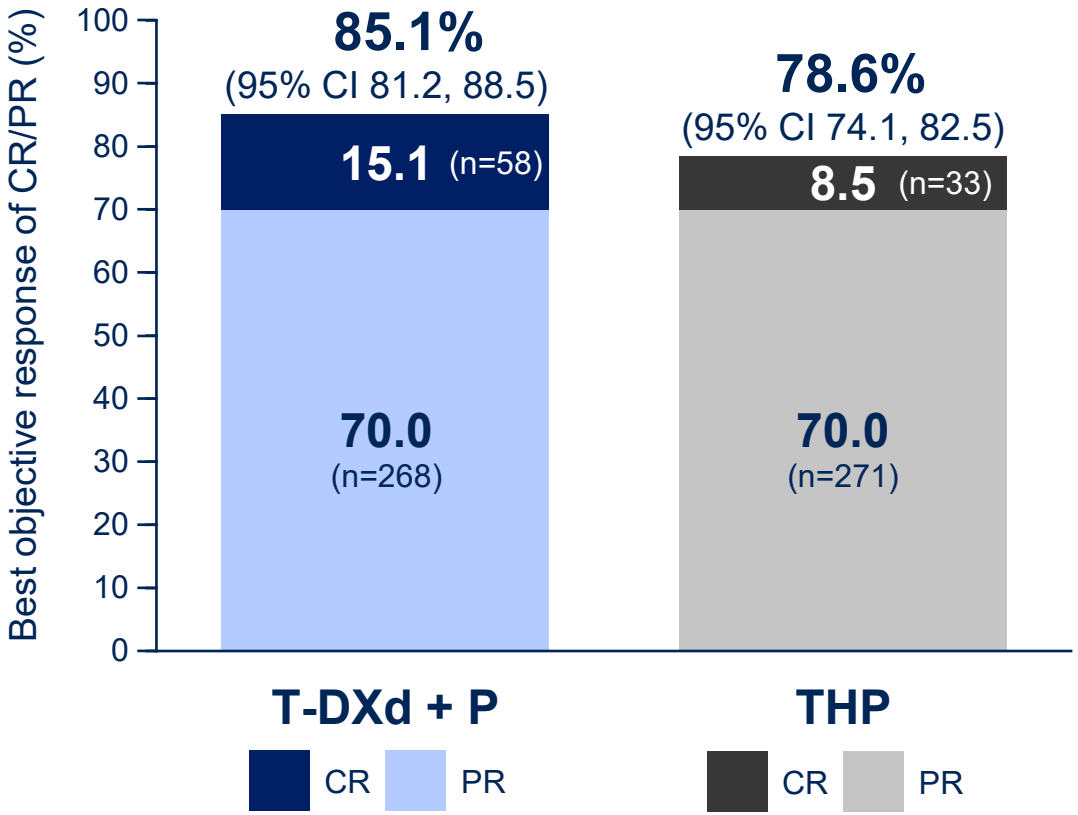


Size of circle is proportional to the number of events
BICR, blinded independent central review;
CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor;
NC, not calculable; P, pertuzumab;
(m)PFS, (median) progression-free survival;
T-DXd, trastuzumab deruxtecan;
THP, taxane + trastuzumab + pertuzumab

PFS benefit with T-DXd + P vs THP was consistently observed across prespecified subgroups, including stratification factors

DB09 ORR and DOR (BICR)

Confirmed ORR*



	T-DXd + P (n=383)	THP (n=387)
Median DOR, mo (95% CI)	39.2 (35.1, NC)	26.4 (22.3, NC)
Remaining in response at 24 mo (%)	73.3	54.9
Stable disease, n (%)	38 (9.9)	56 (14.5)

Response rates were greater with T-DXd + P vs THP and were durable

*Based on RECIST v1.1; response required confirmation after 4 weeks
BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; mo, months; NC, not calculable; ORR, objective response rate; P, pertuzumab; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; THP, taxane + trastuzumab + pertuzumab

DB09: T-DXd + Pertuzumab

- Median Progression Free Survival of 40.7 mos is historic!
  - THP in CLEOPATRA median PFS only 18.6 mos
  - THP in this study notably longer at 26 mos (endocrine therapy used during maintenance phase)
  - Likely will receive approval
  - But….

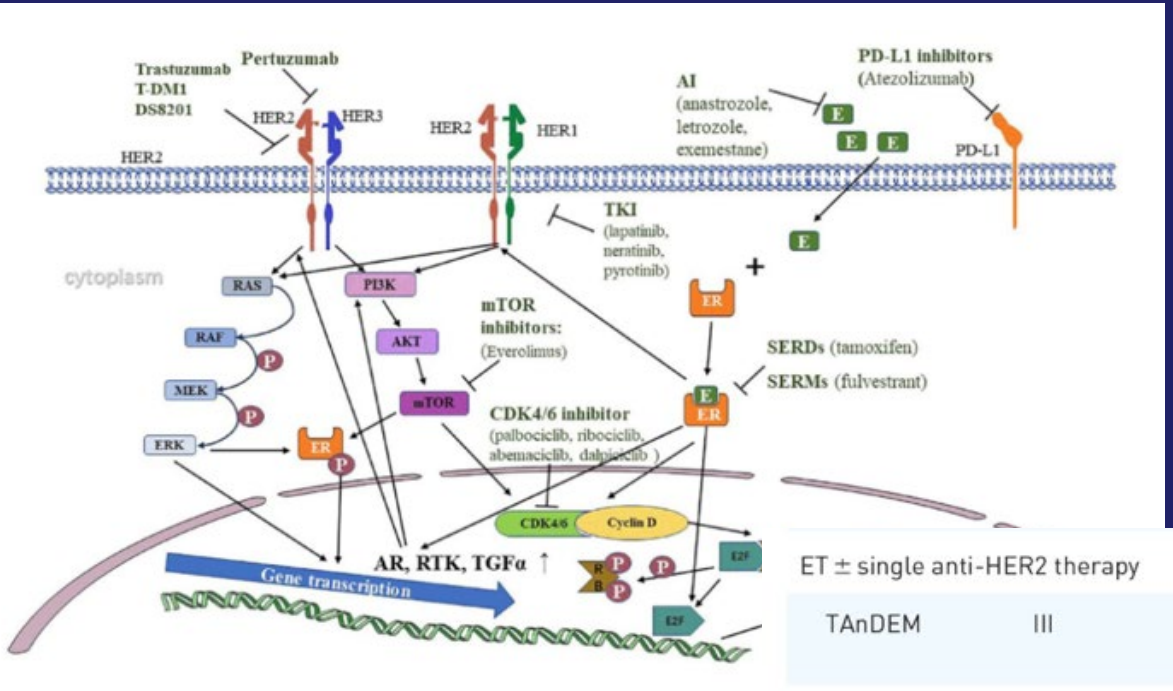
Is Frontline T-DXd/Pertuzumab necessary for everyone?

- Overall survival benefit not yet seen
- Unclear whether pertuzumab is adding anything to the T-DXd
- Very few patients crossed over so do not know if harming patients by waiting for 2nd line for T-DXd
- 16% of patients on CLEOPATRA were progression free at 8 years. Can we prospectively select those pts and treat them with THP—HP maintenance?
- Studies ongoing (DEMETHER) to evaluate induction T-DXd with maintenance HP strategy (Cortés J, *et al*. SABCS 2024; P5-03-11)

Bernstam FM, Clin Cancer Res 2019;25:2033
Grinda T, et al. ESMO Open. 2021;6:100114.

Focus on HER2+ HR+ Metastatic Disease

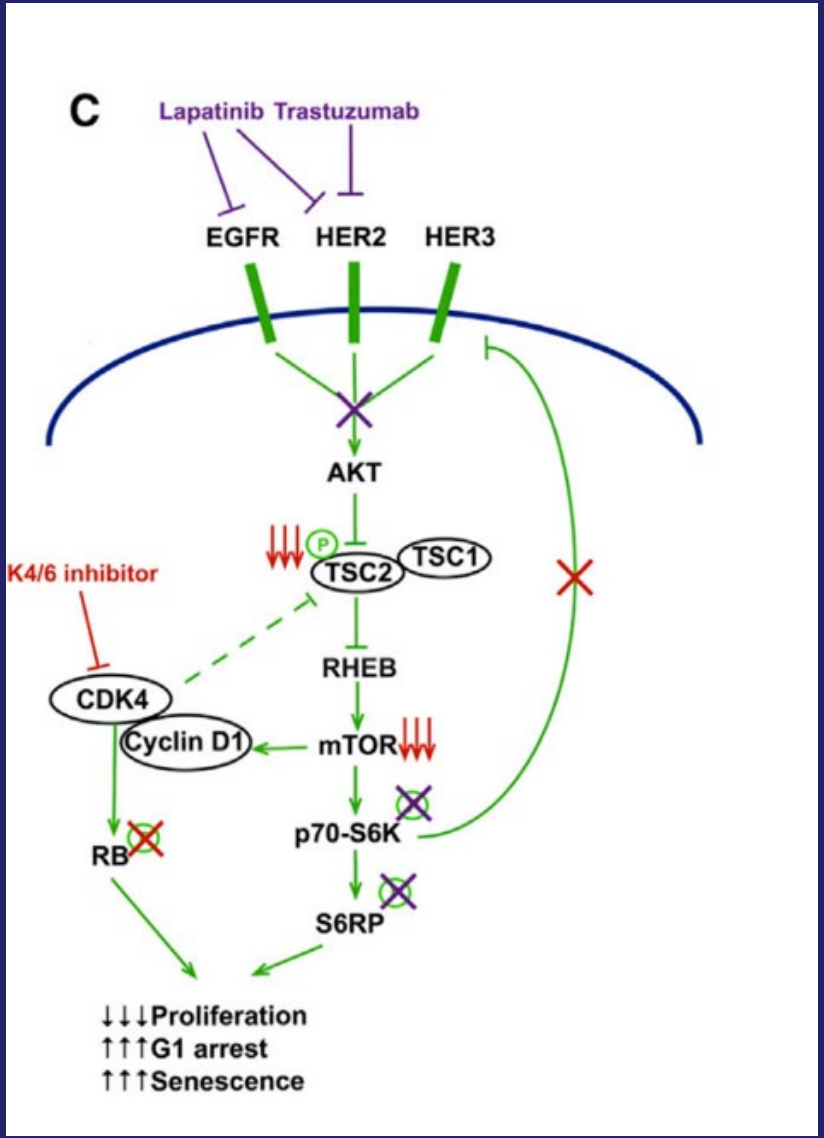
Crosstalk between HER2 and ER pathways



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

Co-treating cells with a CDK4/6i and anti-HER2 therapy is synergistic



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 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)

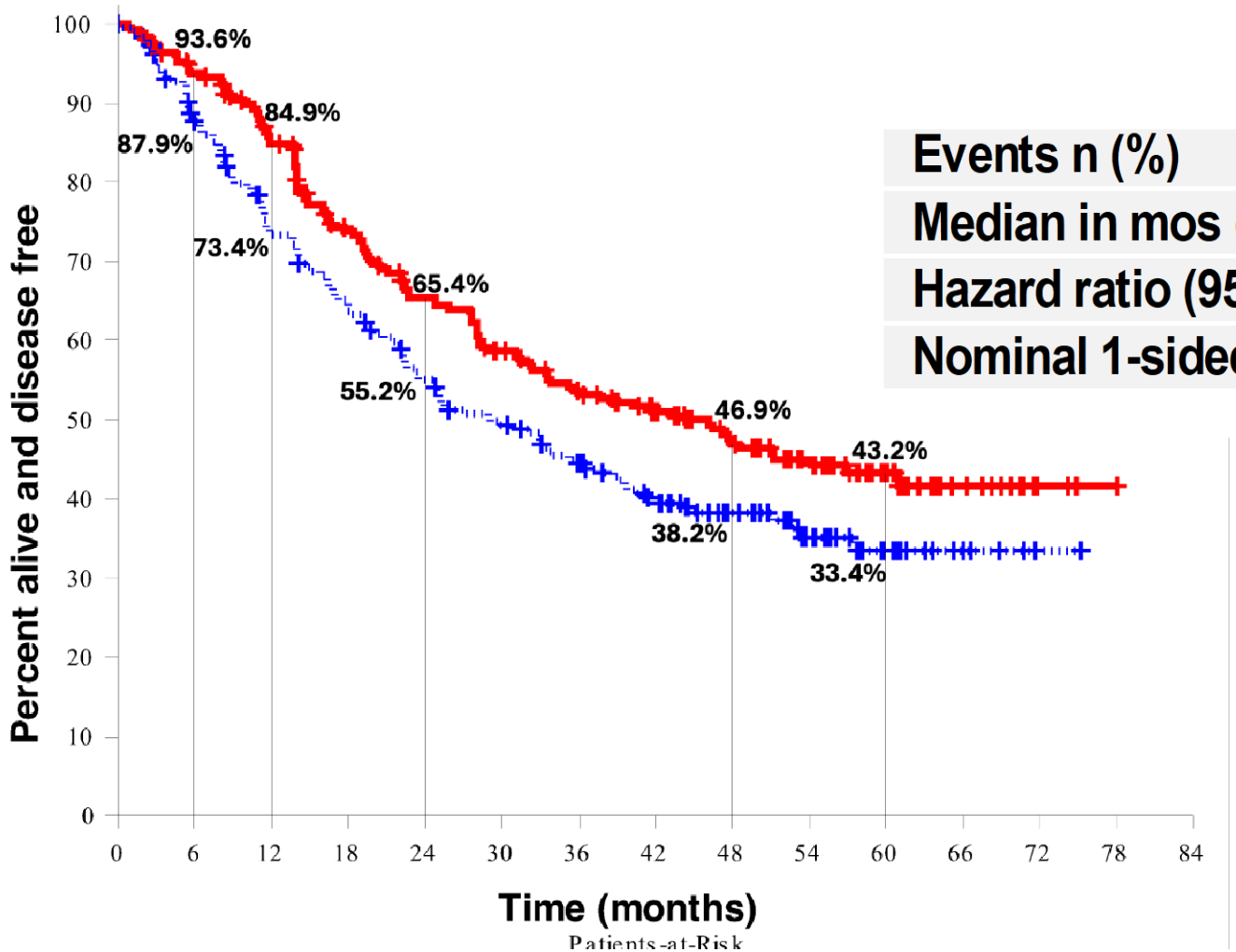
97% used pertuzumab

Prior trastuzumab 71%

ORR 69%

Metzger O et al. SABCS 2024

PATINA 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!

Metzger O et al. SABCS 2024

AFT-38 PATINA

Pre-Study

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Trastuzumab ± Pertuzumab + Endocrine therapy†

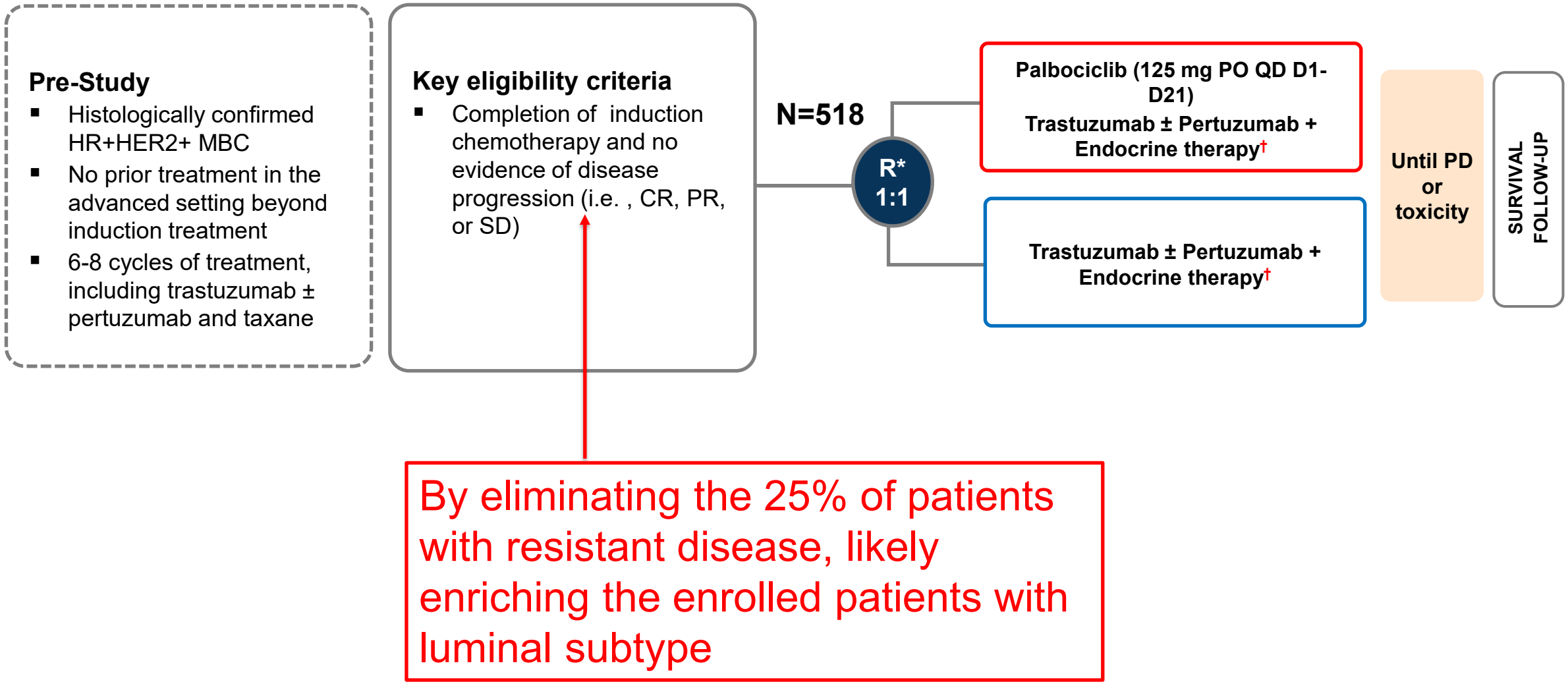
Until PD or toxicity

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

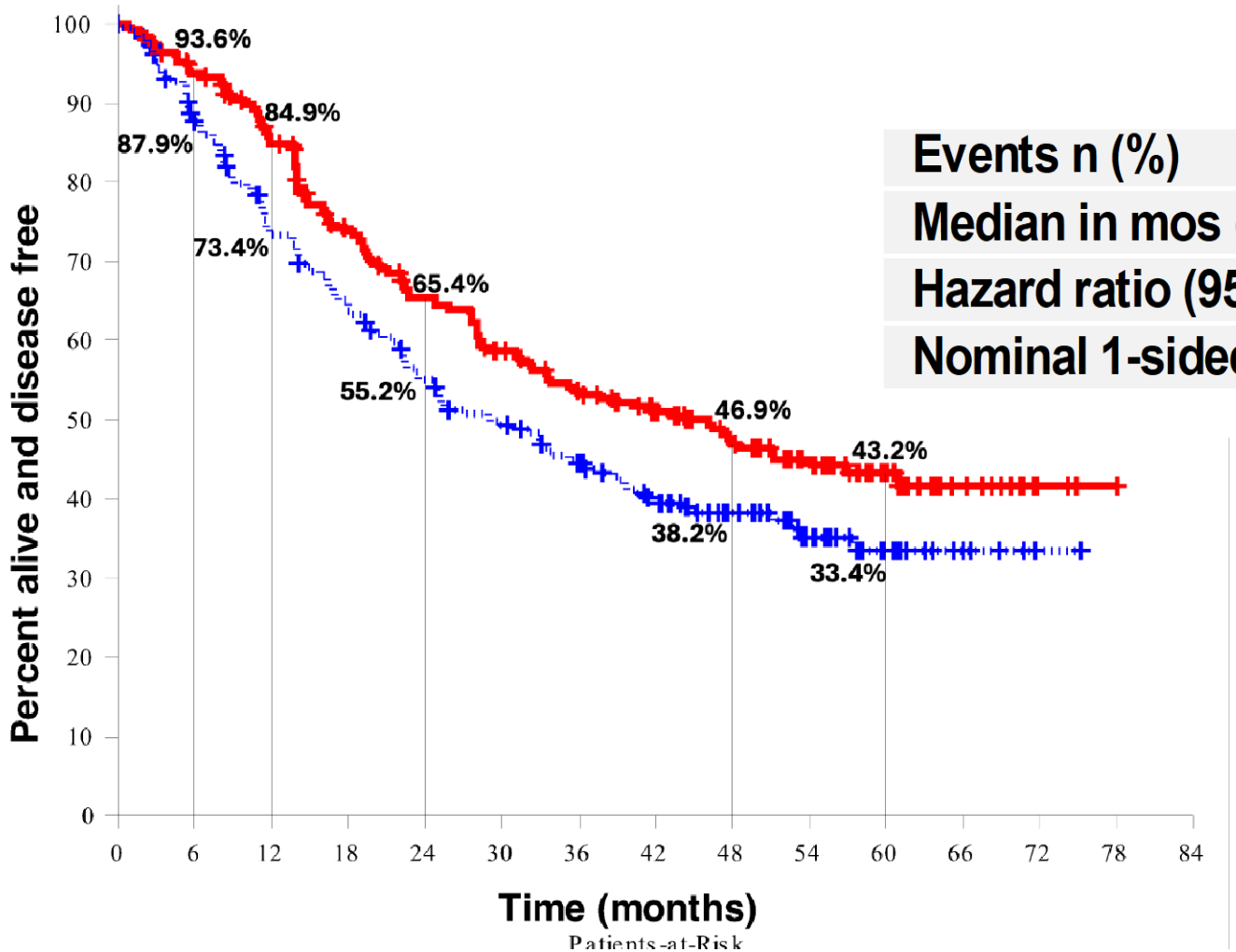
Metzger O et al. SABCS 2024

AFT-38 PATINA



Metzger O et al. SABCS 2024

Investigator-Assessed PFS



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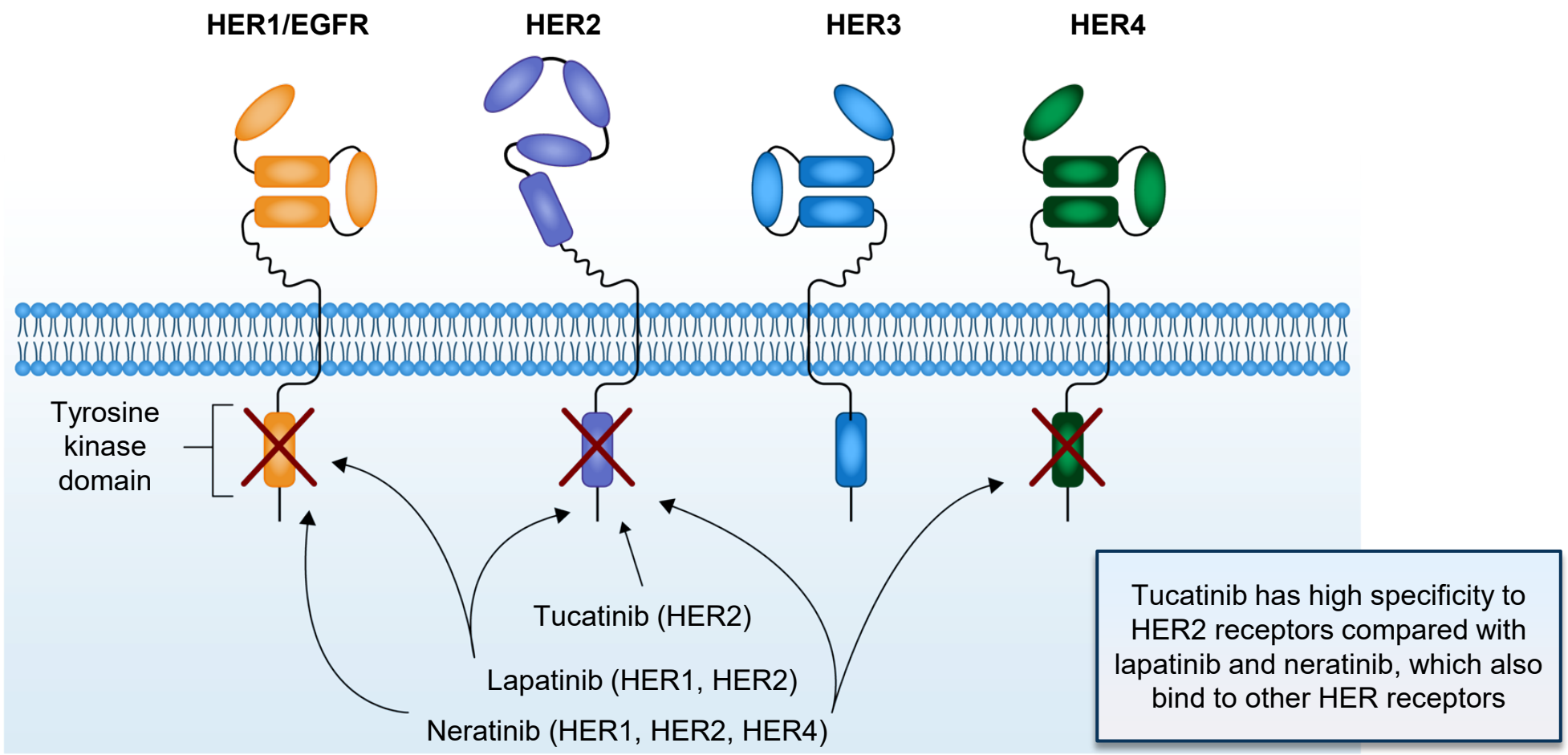
Hazard ratio (95% CI)	0.74 (0.58–0.94)	
Nominal 1-sided *P* value	0.0074	

This is impressive! (some would say, historic?!)

Metzger O et al. SABCS 2024

HER2-Targeted Tyrosine Kinase Inhibitors[1,2]



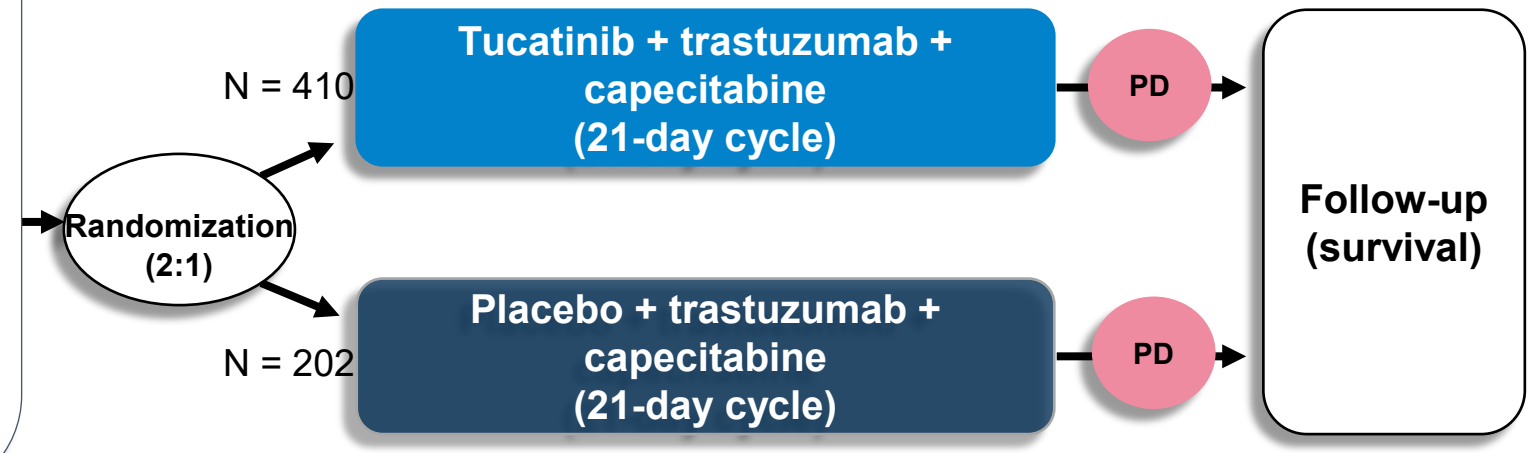
1. Dent SF, et al. Curr Oncol Rep. 2021;23:128. 2. Murthy R, et al. Lancet Oncol. 2018;19:880-888.

HER2CLIMB

Tucatinib + Trastuzumab + Capecitabine vs Placebo + Trastuzumab + Capecitabine

Inclusion criteria

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



Stratification variables

- Presence of brain metastases (yes/no)
- ECOG status (0 or 1)
- Region of the world (US or Canada or rest of world)

Endpoints

- Primary: PFS (first 480 patients randomized)
- Secondary: OS (total population), PFS among patients with brain metastases, ORR

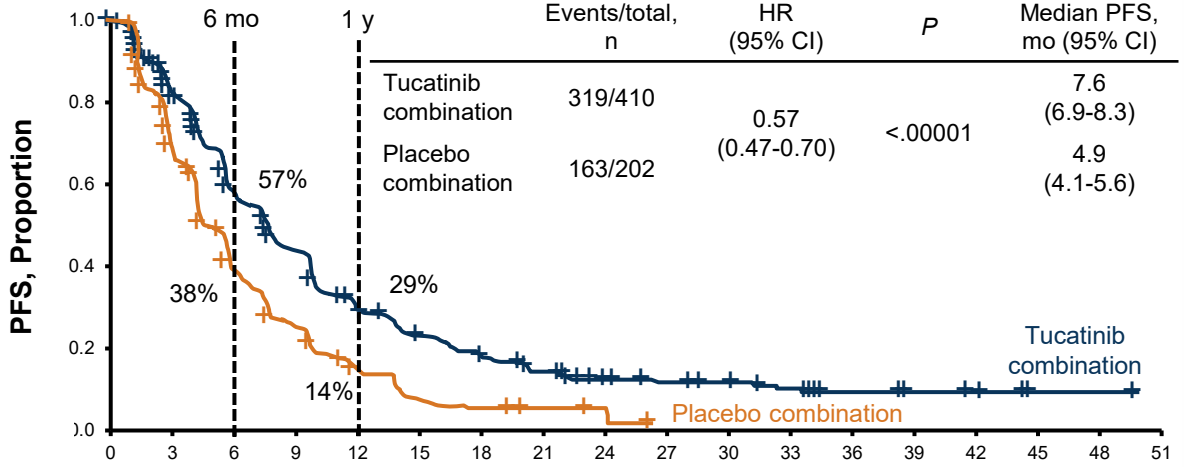
Notable baseline characteristic: *48% of patients had CNS metastases*

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

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

HER2CLIMB: PFS and OS[1] with tucatinib/capecitabine/trastuzumab

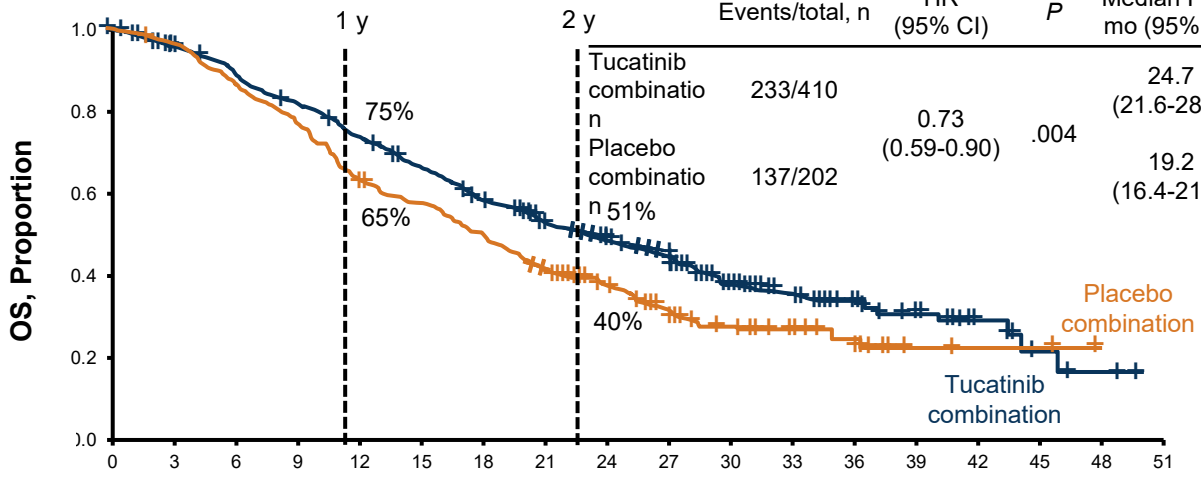
PFS



	Events/total, n	HR (95% CI)	*P*	Median PFS, mo (95% CI)
Tucatinib combination	319/410	0.57 (0.47-0.70)	<.00001	7.6 (6.9-8.3)
Placebo combination	163/202			4.9 (4.1-5.6)

No. at Risk																		
Tucatinib combination	410	303	205	154	99	77	59	44	28	24	20	14	9	5	4	1	1	0
Placebo combination	202	118	64	41	19	9	6	4	2	0	0	0	0	0	0	0	0	0

OS



	Events/total, n	HR (95% CI)	*P*	Median PFS, mo (95% CI)
Tucatinib combination	233/410	0.73 (0.59-0.90)	.004	24.7 (21.6-28.9)
Placebo combination	137/202			19.2 (16.4-21.4)

No. at Risk																		
Tucatinib combination	410	387	356	325	295	268	241	214	153	122	81	56	38	24	19	11	4	2	0
Placebo combination	202	191	174	156	129	114	103	87	63	47	28	21	14	8	4	3	2	0	0

1. Curigliano G et al. *Ann Oncol*. 2022;33:321-329.

Fred Hutch Cancer Center

HER2+ Brain Metastases

Discussion: Should We Screen Asymptomatic Patients With HER2+ MBC for BMs?

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

"There are insufficient data to recommend for or against performing routine magnetic resonance imaging to screen for brain metastases; clinicians should have a low threshold for MRI of the brain because of the high incidence of brain metastases among patients with HER2+ advanced breast cancer."

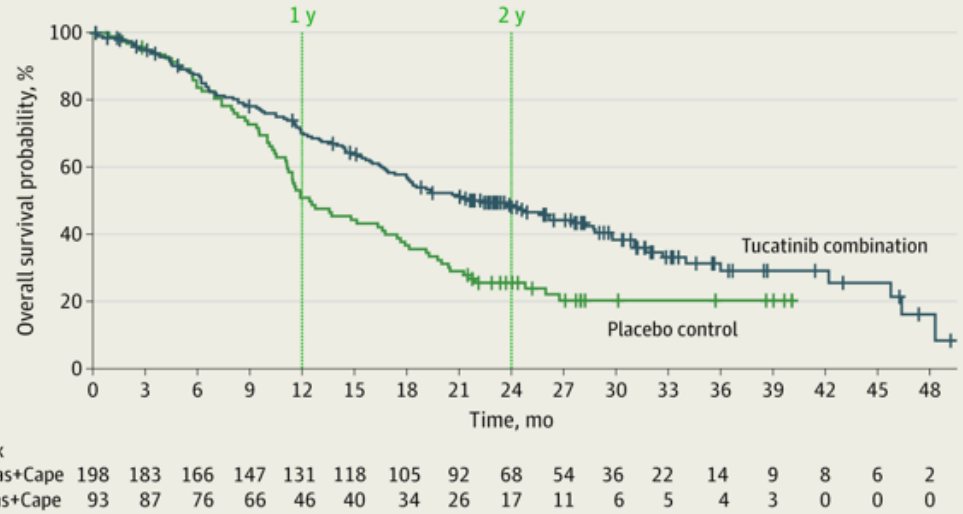
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

"Screening at diagnosis is potentially justified in HER2+ and TN MBC (EANO: IV, n/a; ESMO IV, B). This approach will result in a higher rate of detection of asymptomatic BM."

Outcomes in HER2CLIMB in patients with CNS metastases

FINDINGS

Median OS was longer in the tucatinib-combination group compared with the placebo-combination group



Median OS:

21.6 mo (95% CI, 18.1-28.5 mo) in tucatinib-combination group

12.5 mo (95% CI, 11.2-16.9 mo) in placebo-combination group

Table. Confirmed Intracranial Responses in Patients With Active Brain Metastases and Measurable Intracranial Lesions at Baseline

Intracranial response	Tucatinib combination (n = 55)[a]	Placebo combination (n = 20)[b]
Patients with objective response of confirmed complete response or partial response, No.	26	4
Confirmed ORR-IC, % (95% CI)	47.3 (33.7-61.2)	20.0 (5.7-43.7)
DOR-IC, median (95% CI), mo[c]	8.6 (5.5-10.3)	3.0 (3.0-10.3)

Abbreviations: DOR-IC, duration of intracranial response; ORR-IC, intracranial objective response rate.

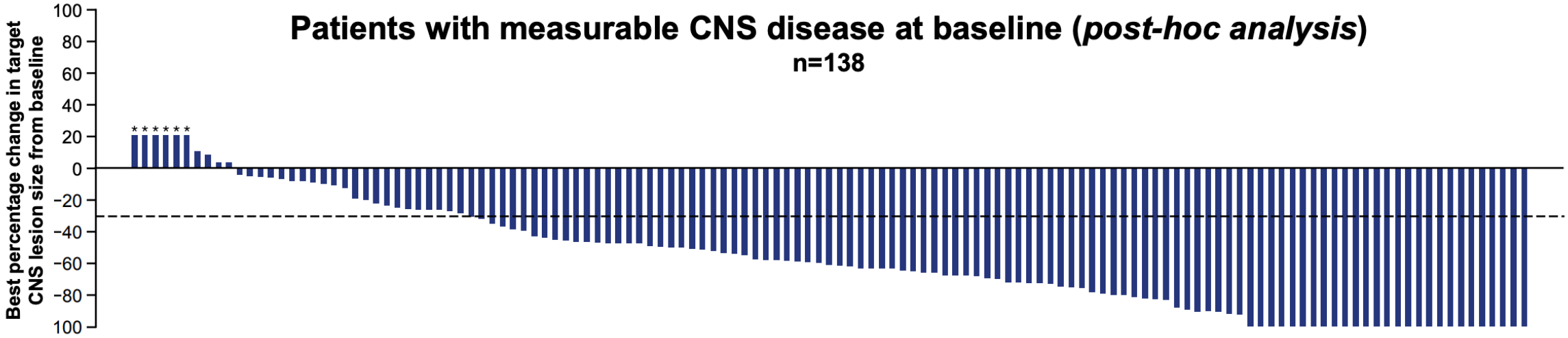
[a] Tucatinib, trastuzumab, and capecitabine.

[b] Placebo, trastuzumab, and capecitabine.

[c] Calculated with the complementary log-log transformation method.

Lin, et al. JAMA Oncol. 2023;9(2):197-205. doi:10.1001/jamaoncol.2022.5610

DESTINY-Breast12: T-DXd in Patients with CNS metastases
Baseline BMs: CNS ORR[1]



Measurable CNS disease at baseline	All patients (n=138)	Stable BMs (n=77)	Active BMs (n=61)	Active BM subgroups: Untreated (n=23) *Post-hoc analysis*	Active BM subgroups: Previously treated / progressing (n=38) *Post-hoc analysis*
Confirmed CNS ORR, % (95% CI)	**71.7 (64.2, 79.3)**	79.2 (70.2, 88.3)	62.3 (50.1, 74.5)	82.6 (67.1, 98.1)	50.0 (34.1, 65.9)

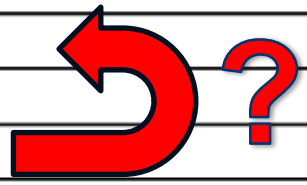
T-DXd showed substantial CNS responses in the overall BMs population, including patients with stable and active BMs

Dashed line indicates a 30% decrease in target tumor size (PR). *Imputed values: a value of +20% was imputed if best percentage change could not be calculated because of missing data if: a patient had a new lesion or progression of non-target lesions or target lesions, or had withdrawn because of PD and had no evaluable target lesion data before or at PD.

1. Lin N et al. ESMO 2024. Abstract LBA18.

Summary: Standard for HER2+ MBC

HR-Positive or -Negative and HER2-Positive[m]	
See BINV-Q (1) for Considerations for systemic HER2-targeted therapy.	
Setting	**Regimen**
First Line[n]	Pertuzumab + trastuzumab + docetaxel (category 1, preferred)
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second Line[o]	Fam-trastuzumab deruxtecan-nxki[n] (category 1, preferred)
Third Line	Tucatinib + trastuzumab + capecitabine[o] (category 1, preferred)
	Ado-trastuzumab emtansine (T-DM1)[p]
Fourth Line and Beyond (optimal sequence is not known)[q]	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents[r,s]
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
	Abemaciclib in combination with fulvestrant and trastuzumab (for HR+ only) (category 2B)
	Targeted Therapy and emerging biomarker Options BINV-Q (7) and BINV-Q (8)



HER2+ Brain Metastases: NCCN Guidelines v2.2025

- HER2 positive
  - Preferred
    - Tucatinib + trastuzumab + capecitabine (category 1) if previously treated with ≥1 regimen[6]
    - Fam-trastuzumab deruxtecan-nxki if previously treated with ≥1 regimen[7,8]
  - Other Recommended
    - Ado-trastuzumab emtansine (T-DM1)[9]
    - Neratinib and T-DM1[10]
    - Capecitabine + lapatinib[11,12]
    - Capecitabine + neratinib[13,14]
    - Pertuzumab and high-dose trastuzumab[d,15]
    - Paclitaxel + neratinib (category 2B)[16]

Summary: Standard for HER2+ MBC

First Line

Trastuzumab + pertuzumab + taxane

CLEOPATRA

- Continue HP after induction
- HR+: Consider addition of palbociclib and endocrine therapy to HP (PATINA trial)

Second Line

Trastuzumab deruxtecan (T-DXd)

DB03

or

Tucatinib + trastuzumab + capecitabine

HER2CLIMB

Factors include extracranial disease burden, intracranial disease burden, comorbidities, patient preference

Third Line

Tucatinib + trastuzumab + capecitabine

HER2CLIMB

or

Trastuzumab deruxtecan

DB02/03

or

Trastuzumab emtansine (T-DM1)

EMILIA, TH3RESA

Late Line Options for HER2+ MBC: “Dealer’s Choice”

Fourth Line +

- Trastuzumab emtansine (T-DM1) — TH3RESA
- Margetuximab + chemo — SOPHIA
- Neratinib + capecitabine — NALA
- Trastuzumab + chemo
- Trastuzumab + lapatinib — EGF104900

Many possible agents, including

- Vinorelbine
- Eribulin
- Gemcitabine
- Doxil
- Carboplatin

Special consideration in HR+/HER2+:
fulvestrant/abema/trastuzumab

Or tucatinib/capecitabine/trastuzumab, or T-DXd if not already received

Discussion