The evolving treatment paradigm in HER2+ early breast cancer

Javier Cortés MD PhD
IBCC, International Breast Cancer Center, Pangaea Oncology, Quironsalud Group, Barcelona & Madrid
Fundación Contigo Contra el Cáncer de la Mujer
Medica Scientia Innovation Research (MedSIR), Barcelona, Spain & New Jersey, US

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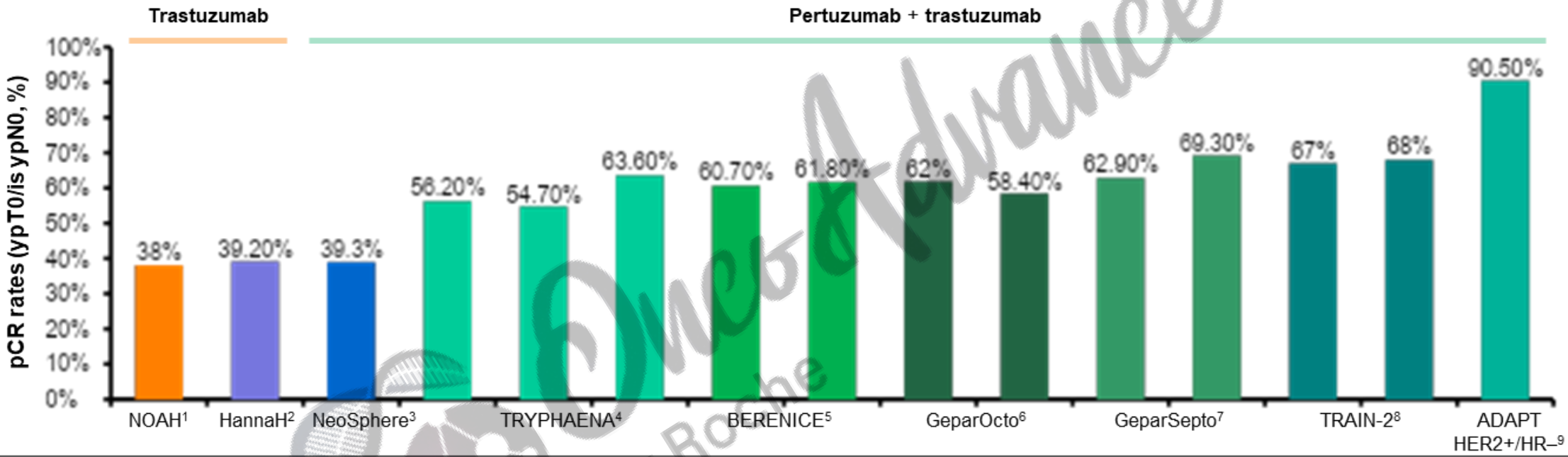
Patents:

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

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

Can we escalate treatment into the routine practice

Neoadjuvant Chemotherapy with Combined Pertuzumab and Trastuzumab Improves pCR Compared to Trastuzumab



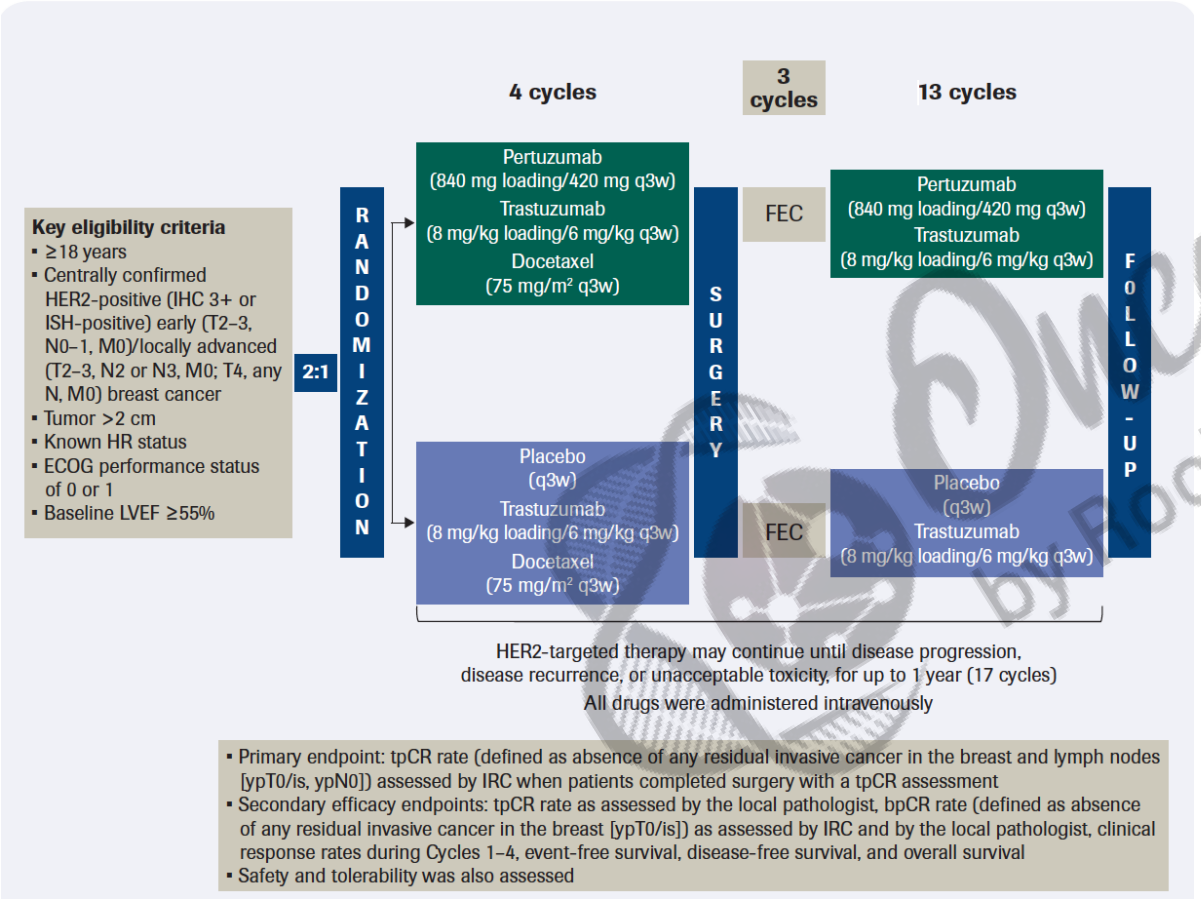
Phase	III[1]	III[2]	II[3]	II[4]			II[5]		III[6]		III[7]		III[8]		II[9]
n*	117	260	107	73	75	77	201	199	192	190	197	199	212	206	42
Regimen	AT+H – T+H – CMF+H	Doc+H – FEC+H	Doc/PH	FEC-Doc/PH	FEC-Doc/PH	Cb/Doc/PH	FEC-Doc/PH	ddAC-Pac/PH	E-TC/PH	Pac/NPLD / Cb/PH	Pac-EC/PH	nabPac-EC/PH	FEC-Pac/Cb/PH	Pac/Cb/PH	Pac weekly/PH
Duration of anti-HER2 therapy	33 weeks	24 weeks	12 weeks	18 weeks	9 weeks	18 weeks	18 weeks	20 weeks	12 weeks	18 weeks	24 weeks		27 weeks		12 weeks

- * n-values represent number of patients in particular treatment arm.

- 1. Gianni L, *et al*. *Lancet* 2010; 2. Ismael G, *et al*. *Lancet Oncol* 2012; 3. Gianni L, *et al*. *Lancet Oncol* 2012; 4. Schneeweiss A, *et al*. *Ann Oncol* 2013; 5. Swain SM, *et al*. *Ann Oncol* 2018; 6. Schneeweiss A, *et al*. *Eur J Cancer* 2018 (incl. suppl. info.); 7. Loibl S, *et al*. *Ann Oncol* 2017; 8. van Ramshorst MS, *et al*. *Lancet Oncol* 2018; 9. Nitz UA, *et al*. *Ann Oncol* 2017.

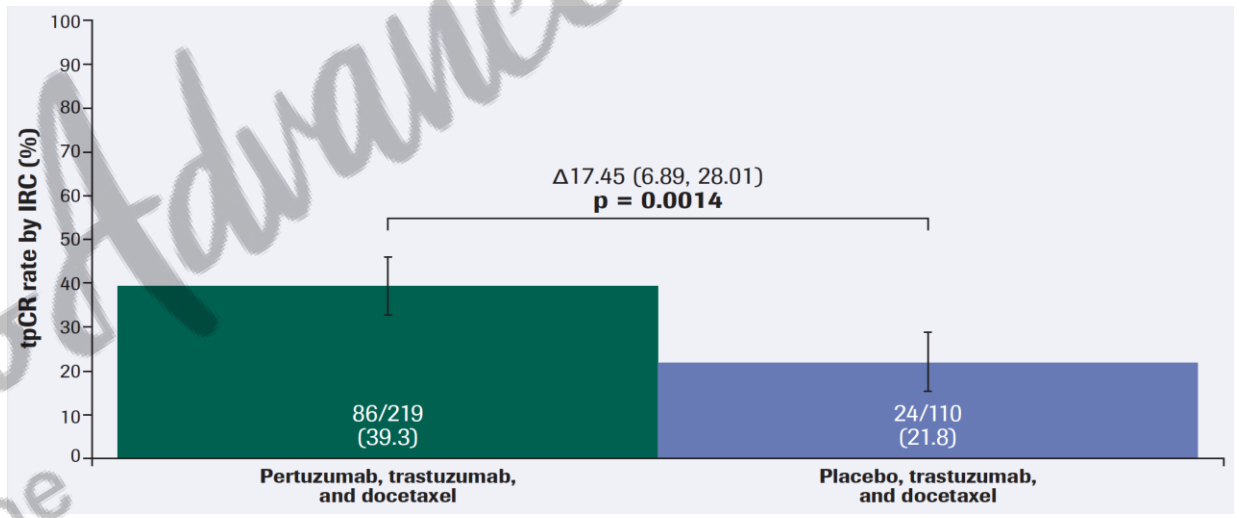
Phase III PEONY Trial: median FU 62.9 months
Neoadjuvant THP vs HP (placebo controlled), Adj FEC then HP or P

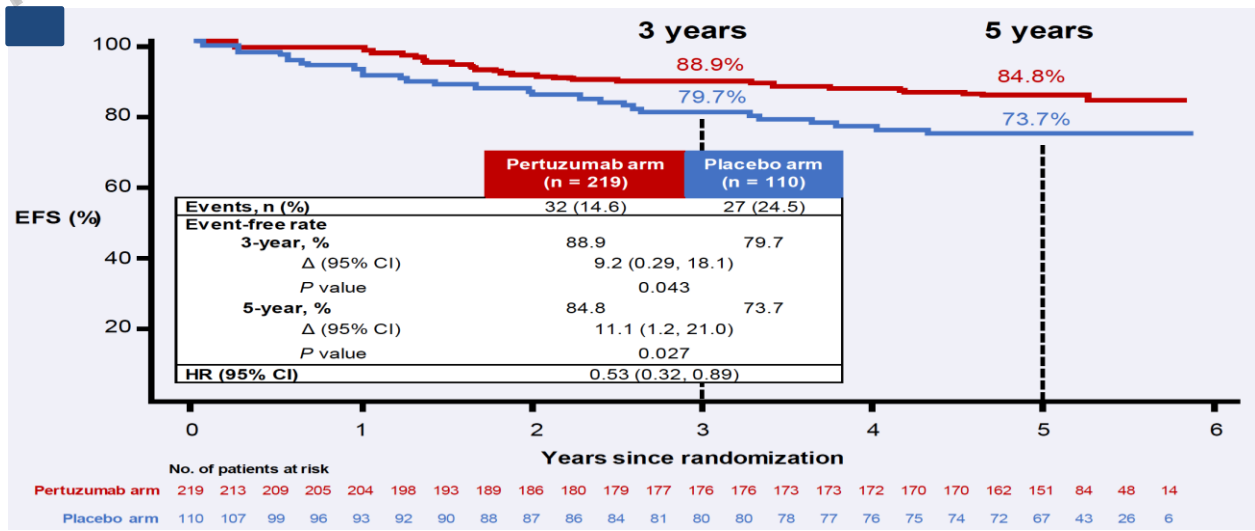
Clinical Trial Design



- Primary endpoint: tpCR rate (defined as absence of any residual invasive cancer in the breast and lymph nodes [ypT0/is, ypN0]) assessed by IRC when patients completed surgery with a tpCR assessment
- Secondary efficacy endpoints: tpCR rate as assessed by the local pathologist, bpCR rate (defined as absence of any residual invasive cancer in the breast [ypT0/is]) as assessed by IRC and by the local pathologist, clinical response rates during Cycles 1–4, event-free survival, disease-free survival, and overall survival
- Safety and tolerability was also assessed

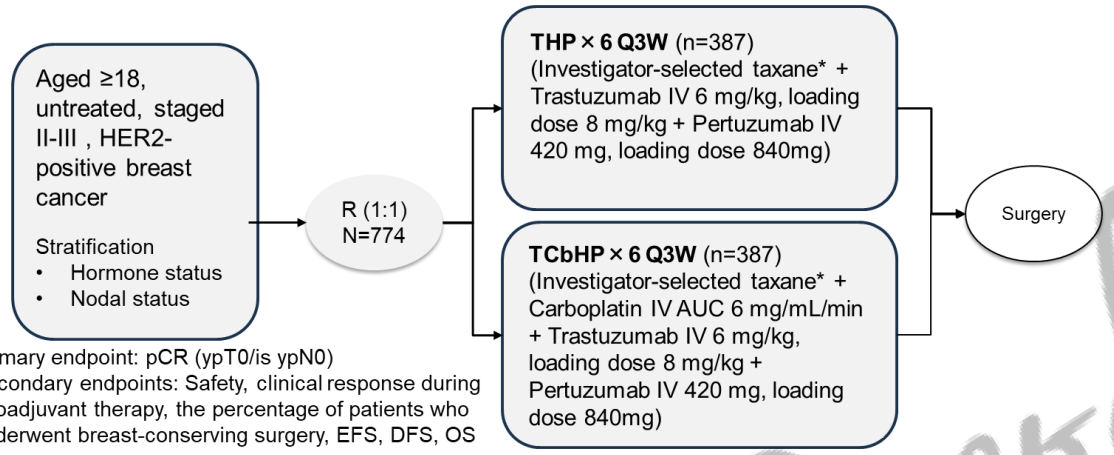
Outcomes





Shao et al, JAMA Onc 2020; SABCS 2022

Can we remove carboplatin as well? neoCARHP Study



- 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

	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%)

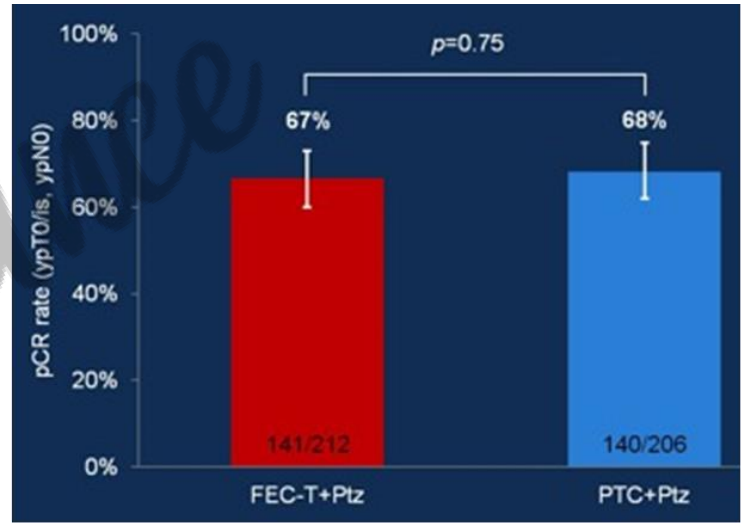
Wang K, et al. ASCO 2025

Can we remove carboplatin as well? neoCARHP Study

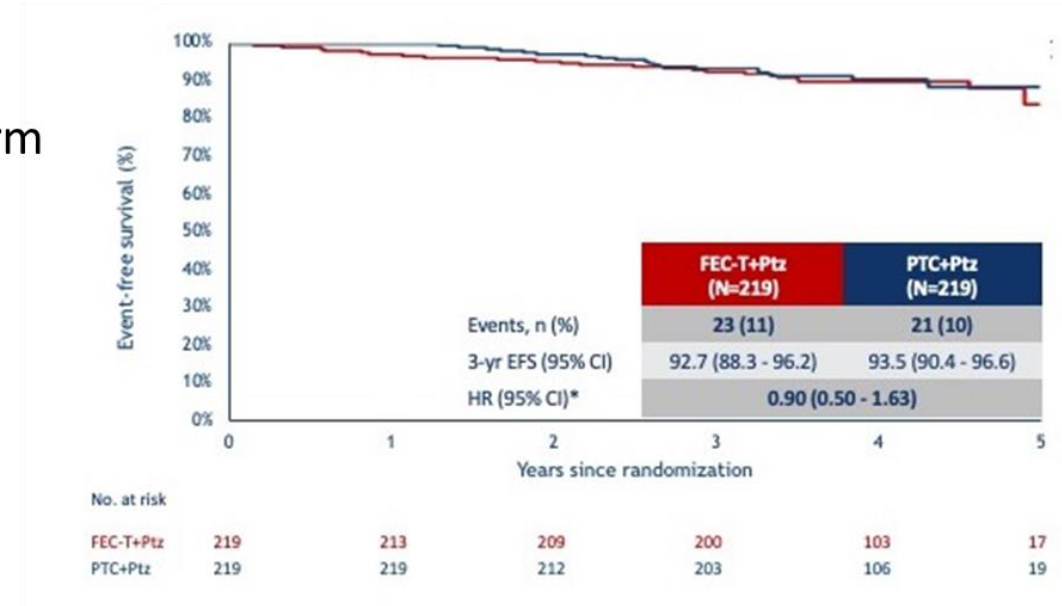
Trial	pCR Overall	pCR in ER-positive	pCR in ER-negative
neoCARHP-TCHP x 6 cy	66%	59%	78%
neoCARHP-THP x 6 cy	64%	56%	78%
TRYPHAENA[1]-TCHP x 6 cy (q3w docetaxel)	64%	50%	84%
TRAIN-2[2]-TCHP x 9 cy (weekly paclitaxel)	68%	55%	84%

Wang K, et al. ASCO 2025; Schneeweiss A, et al. Ann Oncol 2013; Van Ramshorst MS, et al. Lancet Oncol 2018

Can we remove anthracyclines? TRAIN-2 Study



- 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 FN in FEC arm
  - 10% vs 1%
- Significantly less cardiac toxicity with PTC/Ptz
- 2 leukemia in FEC arm



Van Ramshorst MS, et al. Lancet Oncol 2018

Destiny-Breast11 Study design

A randomized, global, multicenter, open-label, Phase 3 study (NCT05113251)

Patient population
- Previously untreated HER2+ eBC
- HR-positive or HR-negative
- High-risk defined as:
  - ≥cT3 and N0−3 or cT0–4 and N1−3
  - Inflammatory BC

Randomized 1:1:1

- n=321 → **T-DXd* → THP†** 4 + 4 cycles
- n=320 → **ddAC‡ → THP§** 4 + 4 cycles
- n=286 → **T-DXd*** 8 cycles

→ **Surgery ¶**

Recommended post-neoadjuvant treatment per study protocol‖

pCR: radiotherapy and concomitant trastuzumab ± pertuzumab for up to 1 year

No pCR: radiotherapy and T-DM1 for up to 14 cycles

HR-positive: endocrine therapy

Data cutoff: March 12, 2025

Primary endpoint
- pCR (ypT0/is ypN0) by blinded central review

Secondary endpoints
- pCR (ypT0 ypN0) by blinded central review
- EFS
- Safety
- Pharmacokinetics and immunogenicity
- Invasive disease-free survival
- Overall survival
- Health-related quality of life

Additional outcome measures
- Residual cancer burden (RCB)

Stratification factors
- HR status: ER and/or PR-positive or negative
- HER2 status: (IHC 3+ or ISH+ in the absence of IHC 3+ status)

The T-DXd alone arm closed on March 13 2024, following Independent Data Monitoring Committee recommendation
The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery

High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if ILD/pneumonitis was suspected while receiving T-DXd, treatment was interrupted and a full investigation completed. Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess left ventricular ejection fraction. *5.4 mg/kg Q3W; †paclitaxel (80 mg/m^2 QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ‡doxorubicin (60 mg/m^2 Q2W) + cyclophosphamide (600 mg/m^2 Q2W); §paclitaxel (80 mg/m^2 QW) + trastuzumab (8 mg/kg loading dose followed by 6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ¶the recommended window for surgery was 3–6 weeks following administration of the last dose of neoadjuvant study treatment; ‖administered as part of the patient's SOC at the investigator's discretion. cT, clinical tumor stage; ER, estrogen receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH+, in situ hybridization–positive; N, nodal stage; PR, progesterone receptor; QXW, every X weeks; T-DM1, trastuzumab emtansine; ypT0/is ypN0, absence of invasive cancer in the breast and axillary nodes; ypT0 ypN0, absence of invasive and in-situ cancer in the breast and axillary nodes

Harbeck N, et al. ESMO 2025; Harbeck N, et al. Ann Oncol 2025

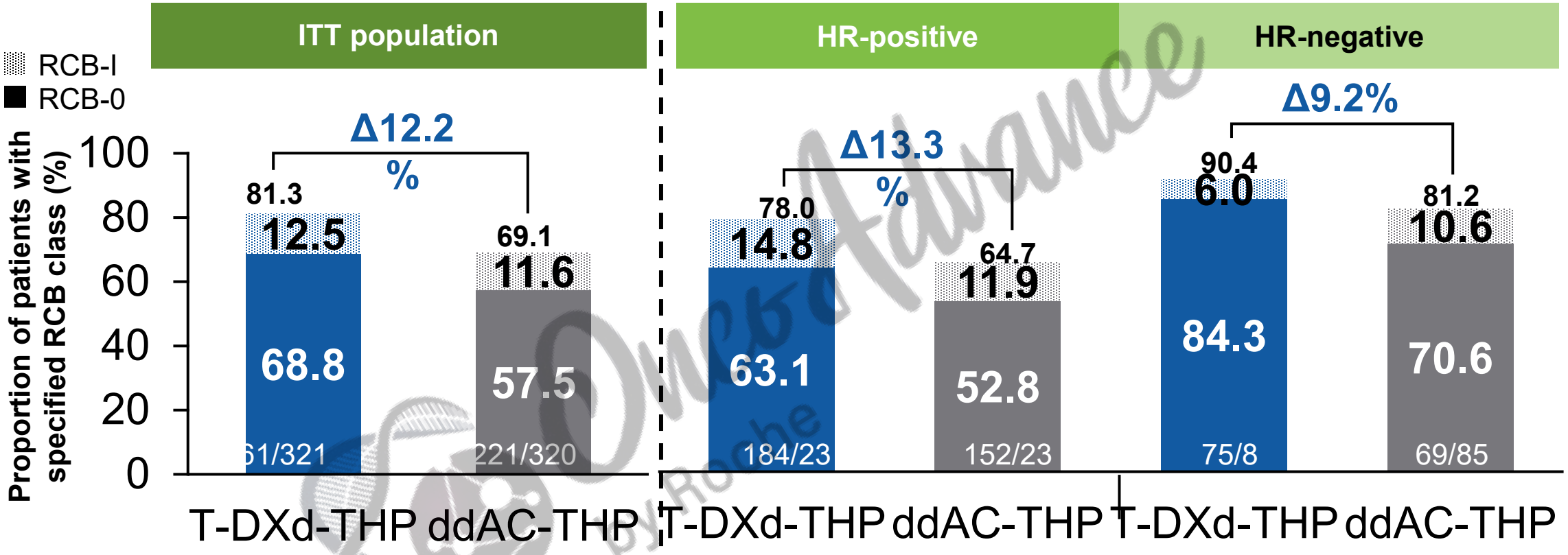
Patient demographics and key baseline characteristics

		T-DXd-THP (n=321)	ddAC-THP (n=320)	T-DXd (n=286)
Median (range) age, years		50 (25–82)	50 (23–79)	50 (23–79)
Female, n (%)		321 (100)	320 (100)	286 (100)
Geographical region, n (%)	Asia	152 (47.4)	152 (47.5)	124 (43.4)
	Western Europe	69 (21.5)	77 (24.1)	66 (23.1)
	North America	43 (13.4)	41 (12.8)	52 (18.2)
	Rest of world*	57 (17.8)	50 (15.6)	44 (15.4)
Race, n (%)†	Asian	160 (49.8)	157 (49.1)	127 (44.4)
	White	140 (43.6)	137 (42.8)	139 (48.6)
	Black or African American	5 (1.6)	7 (2.2)	7 (2.4)
	Other	12 (3.7)	10 (3.1)	8 (2.8)
Eastern Cooperative Oncology Group performance status score, n (%)	0	278 (86.6)	280 (87.5)	252 (88.1)
	1	43 (13.4)	40 (12.5)	34 (11.9)
HER2 status, n (%)‡	IHC 3+	280 (87.2)	283 (88.4)	254 (88.8)
	Other	40 (12.5)	36 (11.3)	32 (11.2)
HR status, n (%)§	Positive¶	236 (73.5)	235 (73.4)	205 (71.7)
Clinical tumor stage, n (%)	cT0–2	176 (54.8)	188 (58.8)	157 (54.9)
	cT3–4	145 (45.2)	132 (41.3)	129 (45.1)
Nodal status, n (%)‖	N0	26 (8.1)	35 (10.9)	20 (7.0)
	N+	287 (89.4)	281 (87.8)	254 (88.8)

*Brazil, Bulgaria, Peru, Poland, Russia, and Saudi Arabia; †not reported for four patients (1.2%), nine patients (2.8%) and five patients (1.7%) in the T-DXd-THP, ddAC-THP, and T-DXd alone arms, respectively; ‡centrally confirmed. Not categorized for one patient (0.3%) in the T-DXd-THP arm and missing for one patient (0.3%) in the ddAC-THP arm; §the proportion of patients with HR-negative disease was capped at 30% to reflect natural prevalence. Missing for two patients (0.6%) and one patient (0.3%) in the T-DXd-THP and T-DXd alone arms, respectively; ¶ER and/or
PR-positive per electronic case report form data; ‖unknown in eight patients (2.5%), four patients (1.3%), and 12 patients (4.2%) in the T-DXd-THP, ddAC-THP, and T-DXd alone arms, respectively

Harbeck N, et al. ESMO 2025; Harbeck N, et al. Ann Oncol 2025

RCB outcomes



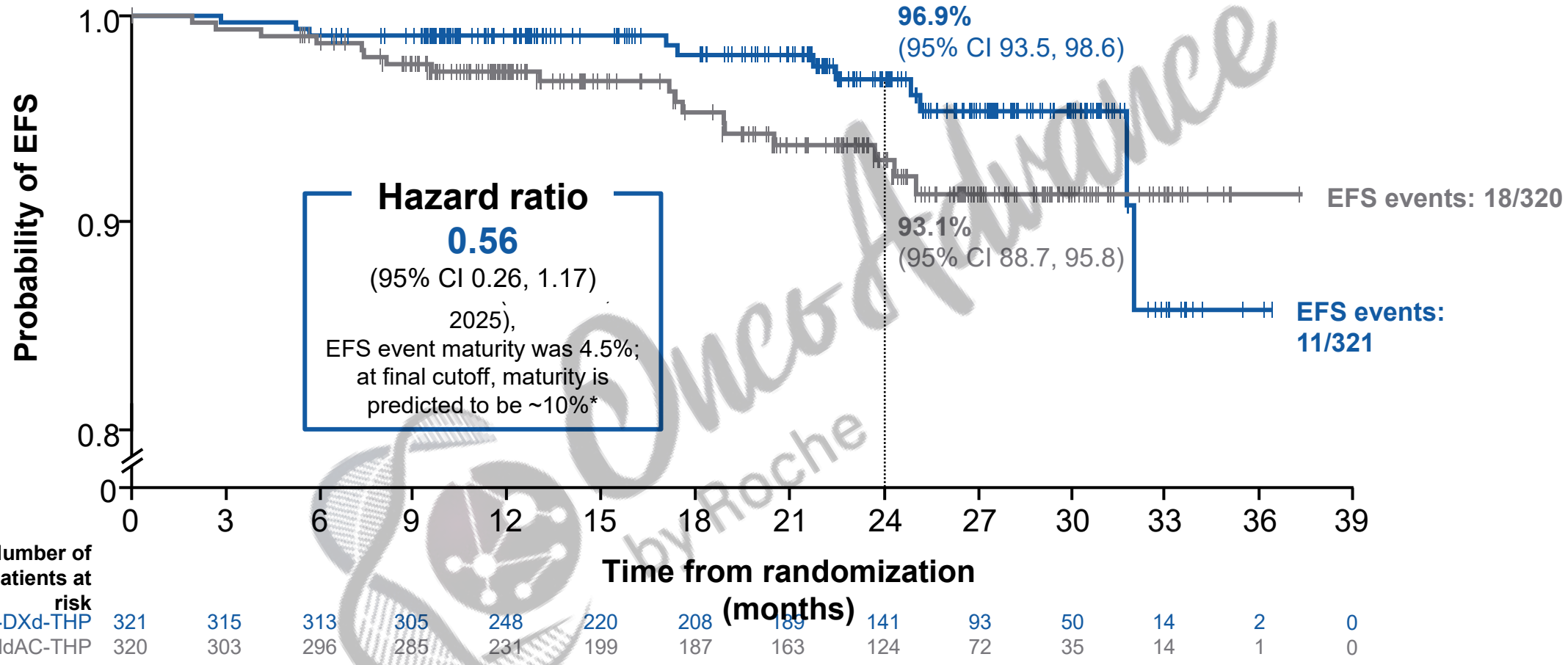
After surgery, 81.3% of patients receiving T-DXd-THP had no or minimal residual invasive cancer (RCB-0+I) detected in the resected breast or lymph node tissue vs 69.1% of those receiving ddAC-THP

Almost 80% of patients with HR-positive disease had RCB-0+I with T-DXd-THP

Unlike pCR results, RCB analysis is based on raw data and is not corrected for patients who did not receive study treatment or any bridging/off study neoadjuvant treatment; therefore, there may be differences between pCR and RCB-0. Not reported in 13 patients (4.0%) in the T-DXd-THP arm and 24 patients (7.5%) in the ddAC-THP arm. RCB class was based on central pathologic evaluation of the residual viable tumor (identified on routine hematoxylin and eosin staining after mapping of the surgical specimen)

Harbeck N, et al. ESMO 2025; Harbeck N, et al. Ann Oncol 2025

EFS



An early positive trend in EFS was observed, favoring T-DXd-THP vs ddAC-THP

The median duration of follow up was 24.3 months with T-DXd-THP and 23.6 months with ddAC-THP. *Predicted maturity assumes that the observed EFS hazard ratio continues after data cutoff (March 12, 2025)

Harbeck N, et al. ESMO 2025; Harbeck N, et al. Ann Oncol 2025

Post-neoadjuvant treatments

n (%)	Patients with pCR*		Patients without pCR*	
	T-DXd-THP (n=226)	ddAC-THP (n=190)	T-DXd-THP (n=95)	ddAC-THP (n=130)
Any adjuvant treatment†	224 (99.1)	187 (98.4)	85 (89.5)	107 (82.3)
Any cytotoxic chemotherapy-containing regimen	13 (5.8)	11 (5.8)	10 (10.5)	12 (9.2)
Any T-DM1-containing regimen	4 (1.8)	4 (2.1)	50 (52.6)	74 (56.9)
Any trastuzumab-containing regimen	213 (94.2)	174 (91.6)	37 (38.9)	34 (26.2)

Post-neoadjuvant treatments were generally well balanced between T-DXd-THP and ddAC-THP arms
In both arms, more than half of patients without pCR received post-neoadjuvant T-DM1

Harbeck N, et al. ESMO 2025; Harbeck N, et al. Ann Oncol 2025

Overall safety summary

n (%)	T-DXd-THP (n=320)*	ddAC-THP (n=312)*
Any AE	314 (98.1)	308 (98.7)
Grade ≥3	120 (37.5)	174 (55.8)
Any serious AE	34 (10.6)	63 (20.2)
AE leading to any dose reduction	58 (18.1)	60 (19.2)
AE leading to any drug interruption	121 (37.8)	170 (54.5)
AE leading to any treatment discontinuation	45 (14.1)	31 (9.9)
Any AE with outcome of death†	2 (0.6)	2 (0.6)
AE of special interest		
Drug-related adjudicated ILD/pneumonitis	14 (4.4)	16 (5.1)
Grade ≥3	2 (0.6)	6 (1.9)
Grade 5	1 (0.3)	1 (0.3)
Left ventricular dysfunction	4 (1.3)	19 (6.1)
Grade ≥3	1 (0.3)	6 (1.9)
Grade 5	0	0
AE leading to surgical delay‡	11 (3.4)	8 (2.6)

The overall safety profile of T-DXd-THP was favorable vs ddAC-THP, with reduced rates of Grade ≥3 AEs, serious AEs, treatment interruptions, and left ventricular dysfunction

ILD incidence was low and similar in both arms

High-resolution computed tomography chest scans were performed every 6 weeks during treatment; if ILD/pneumonitis was suspected while receiving T-DXd, treatment was interrupted and a full investigation completed. Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at end of treatment to assess left ventricular ejection fraction. Median total treatment duration of whole regimen was 24.1 months (T-DXd-THP), and 21.0 months (ddAC-THP). *Safety analyses included all patients who received at least one dose of any study treatment; †T-DXd-THP arm: death of unknown cause (n=1), drug-related pneumonitis adjudicated by the Independent ILD Adjudication Committee (n=1); ddAC-THP arm: investigator-determined drug-related bacterial encephalitis (n=1), drug-related pneumonitis adjudicated by the ILD Adjudication Committee (n=1); ‡defined as surgery not occurring within 3–6 weeks after the last cycle of neoadjuvant treatment

Harbeck N, et al. ESMO 2025; Harbeck N, et al. Ann Oncol 2025

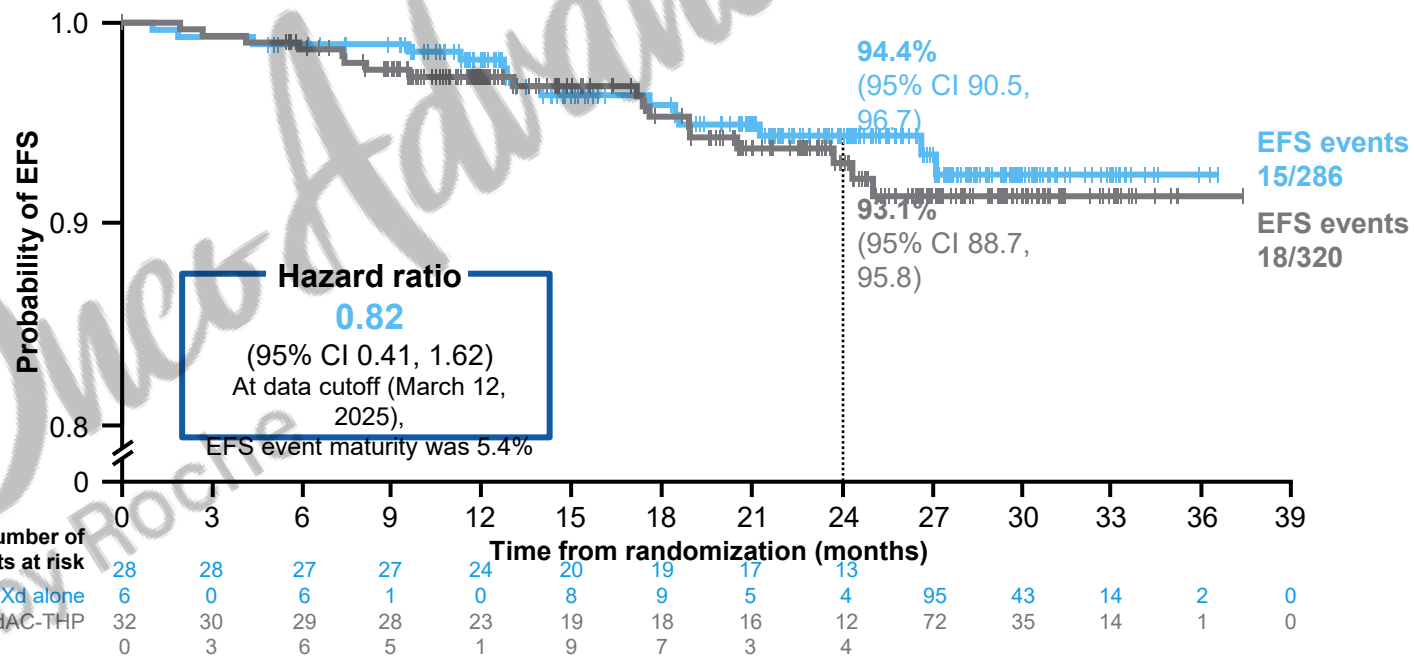
T-DXd alone arm: efficacy summary

On March 13, 2024, the T-DXd alone arm closed following Independent Data Monitoring Committee recommendation.* Patients who were still receiving T-DXd alone could remain on therapy or immediately switch to local SOC

pCR rate

%	T-DXd (n=286)	ddAC-THP (n=320)
Primary analysis Switch to local SOC classified as non-pCR		
pCR†	43.0	56.3
Δ (95% CI)	−13.2 (−20.8, −5.4)	
Prespecified supplementary analysis Switch to local SOC not automatically classified as non-pCR		
pCR†	51.4	57.2
Δ (95% CI)	−5.8 (−13.4, 1.9)	

EFS



T-DXd alone showed inferior but robust pCR compared with the five-agent ddAC-THP
EFS data were similar for T-DXd alone and ddAC-THP

Treatment effects were estimated by the difference in pCR with 95% CIs based on the stratified Miettinen and Nurminen's method, with strata weighting by sample size (ie Mantel–Haenszel weights). Median duration of follow up was 24.9 months (T-DXd) and 23.6 months (ddAC-THP). Analyses are reported in the ITT population. *The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery; †by blinded central review

Harbeck N, et al. ESMO 2025; Harbeck N, et al. Ann Oncol 2025

Eligibility criteria for DESTINY-Breast11 differed from NeoSphere, TRYPHAENA, TRAIN-2 and NeoCARHP[1–6]

- DESTINY-Breast11 enrolled only patients at higher risk of recurrence (T >5 cm and/or N+)[1,2] whereas NeoSphere, TRYPHAENA, TRAIN-2 and NeoCARHP also permitted patients with T2–5 cm and N0 disease to enrol[3–6]

Key eligibility criteria	DESTINY-Breast11[1,2]	NeoSphere[3]	TRYPHAENA[4]	TRAIN-2[5]	NeoCARHP[6]
Disease at presentation	Untreated, high-risk, HER2+ eBC; high risk defined as: • **≥cT3 and N0–3 or cT0–4 and N1–3** • Inflammatory BC	• Operable BC: cT2–3, N0–1, M0 • LABC: cT2–3, N2–3, M0 or T4a–c, any N, M0 • Inflammatory BC: T4d, any N, M0			
Baseline patient characteristics					
HR+	**73%**	47%	51%	58%	63%
N+	**89%**	70%	69%	64%	64%
N0	9%	**29%**	**30%**	36%	36%

Cross-trial comparisons should be interpreted with caution due to differences in study designs and patient populations.

BC, breast cancer; eBC, early breast cancer; H, trastuzumab; HR+, hormone receptor-positive; LABC, locally advanced breast cancer; P, pertuzumab.

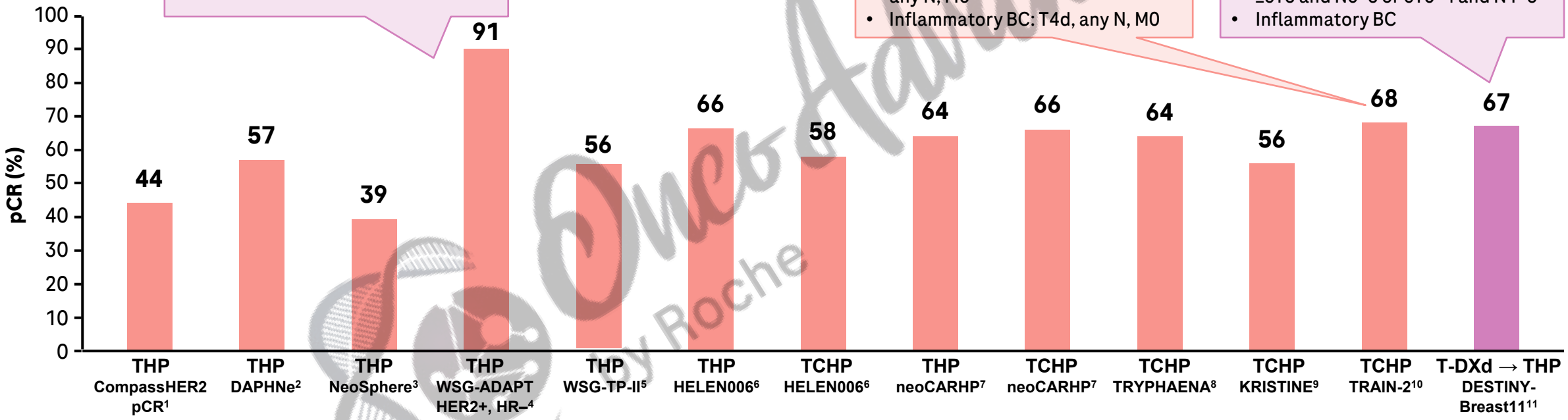
1. Harbeck N, *et al. Ann Oncol* 2025; In press; 2. Harbeck N, *et al.* ESMO 2025 (Oral 291O); 3. Gianni L, *et al. Lancet Oncol* 2012; **13:**25–32; 4. Schneeweiss A, *et al. Ann Oncol* 2013; **00:**1–6; 5. van Ramhorst MS, *et al. Lancet Oncol* 2018; **19:**1630–1640; 6. Gao H-F, *et al.* ASCO 2025 (Oral LBA500).

Perspectives on DESTINY-Breast11:
Can we identify which patients do well on current SoC THP/TCHP?

ADAPT
- cT2+ (or cT1 with cN+)
- cT1-4c, and any clinical nodal status (cN) was permitted

TRAIN-2
- Operable BC: cT2–3, N0–1, M0
- LABC: cT2–3, N2–3, M0 or T4a–c, any N, M0
- Inflammatory BC: T4d, any N, M0

DESTINY-Breast11
Untreated, **high-risk**, HER2+ eBC;
high risk defined as:
- ≥cT3 and N0–3 or cT0–4 and N1–3
- Inflammatory BC



Many patients have good outcomes on THP/TCHP; it is important to define target patient populations based on disease characteristics, risk factors, treatment response and acceptable benefit–risk profiles in the curative setting

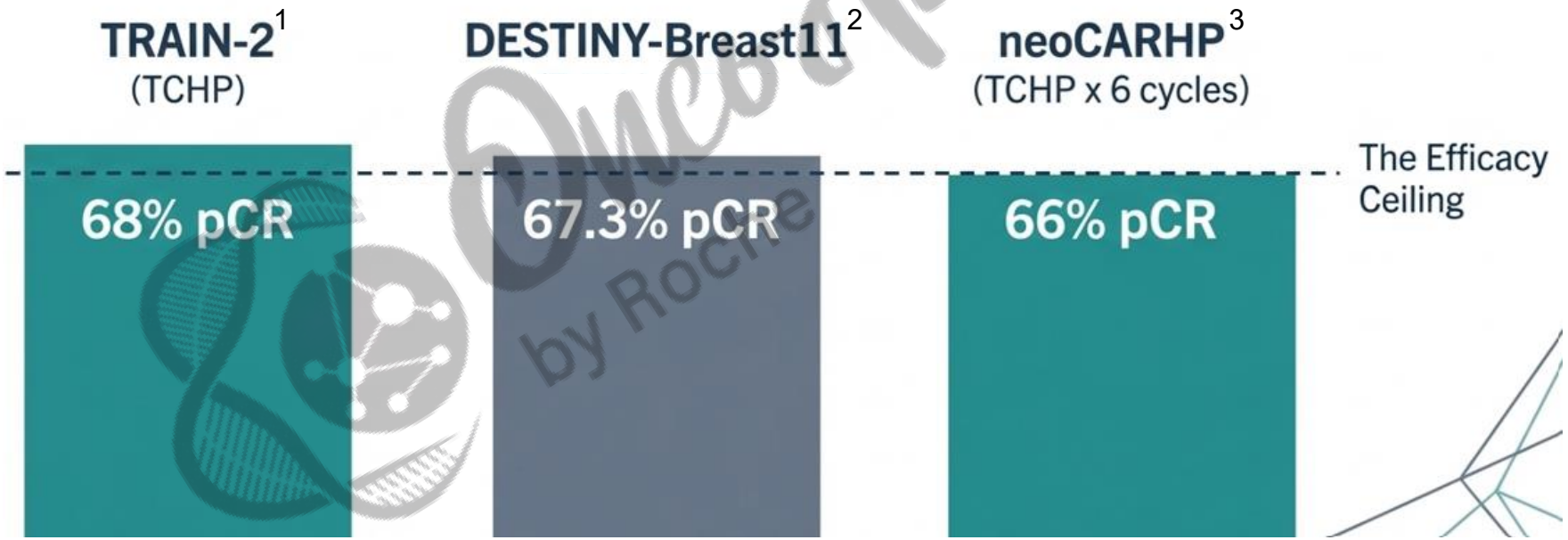
Cross-trial comparisons should be interpreted with caution due to differences in study designs and patient populations.

C, carboplatin; CT, chemotherapy; FEC, 5-flurouracil + epirubicin + cyclophosphamide; H, trastuzumab; P, pertuzumab; pCR, pathological complete response; PH FDC SC, fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection; SoC, standard of care; T, taxane; WSG, West German Study Group.

1. Tung N, *et al.* ASCO 2025 (Oral 501); 2. Waks AG, *et al. npj breast cancer* 2022; **8:**63; 3. Gianni L, *et al. Lancet Oncol* 2012; **13:**25–32; 4. Nitz UA, *et al. Ann Oncol* 2017; **28:**2768–2772; 5. Gluz O, *et al. JAMA Oncol* 2023; **9:**946–954; 6. Chen XC, *et al. Lancet Oncol* 2025; **26:**27–36; 7. Gao H-F, *et al.* ASCO 2025 (Oral LBA500); 8. Schneeweiss A, *et al. Ann Oncol* 2013; **00:**1–6; 9. Hurvitz SA, *et al. Lancet Oncol* 2018; **19:**115–126; 10. van Ramshorst MS, *et al. Lancet Oncol* 2018; **19:**1630–1640; 11. Harbeck N, *et al. Ann Oncol* 2025; In press.

The Neoadjuvant Efficacy Ceiling Has Been Reached

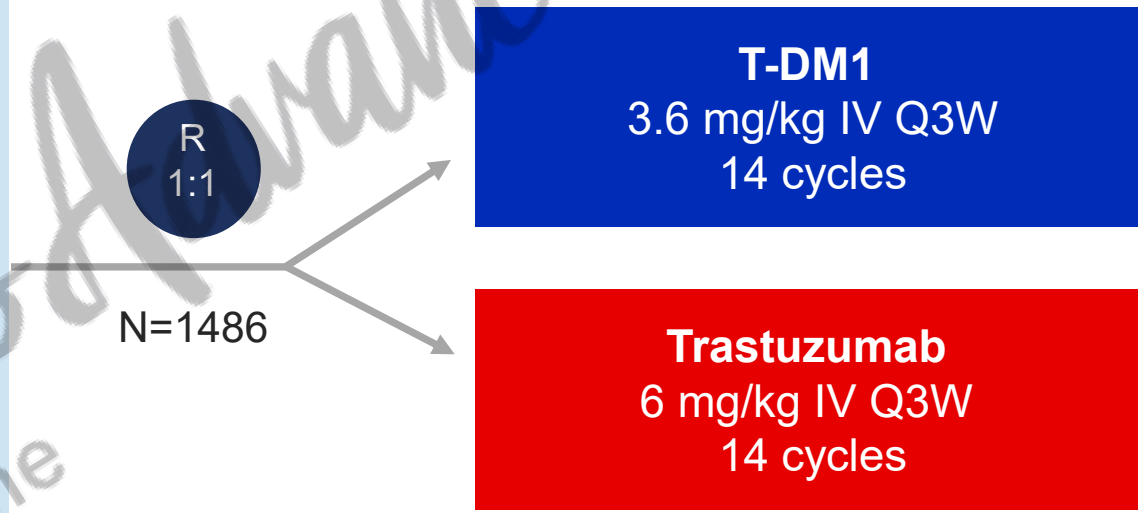
Key Finding: Newer investigational ADC regimen do not meaningfully surpass the high pCR ceiling already established by optimized standard of care regimen of TCHP (Docetaxel, Carboplatin, PHESGO)



1. Van Ramshorst, MS et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2)., Lancet Oncol 2018; 19: 1630–40. **2.** Harbeck N., et al. Neoadjuvant trastuzumab deruxtecan alone or followed by paclitaxel, trastuzumab, and pertuzumab for high-risk HER2-positive early breast cancer (DESTINY-Breast11)., Annals of Oncology. 2025. https://doi.org/10.1016/j.annonc.2025.10.019. **3.** NeoCARHP Study (NCT04858529): De-escalated neoadjuvant taxane plus trastuzumab and pertuzumab with or without carboplatin in HER2-positive early breast cancer. TCbHP (TCHP) Arm Results: pCR 65.9%, Grade 3-4 AEs 34.6%. (Presented at ASCO 2025);

KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 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

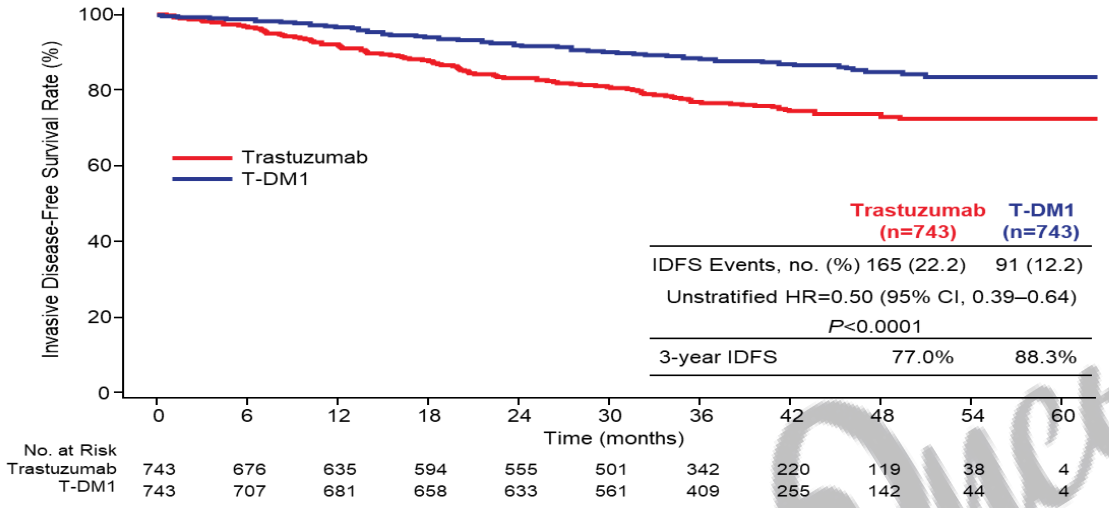
Stratification factors:

- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

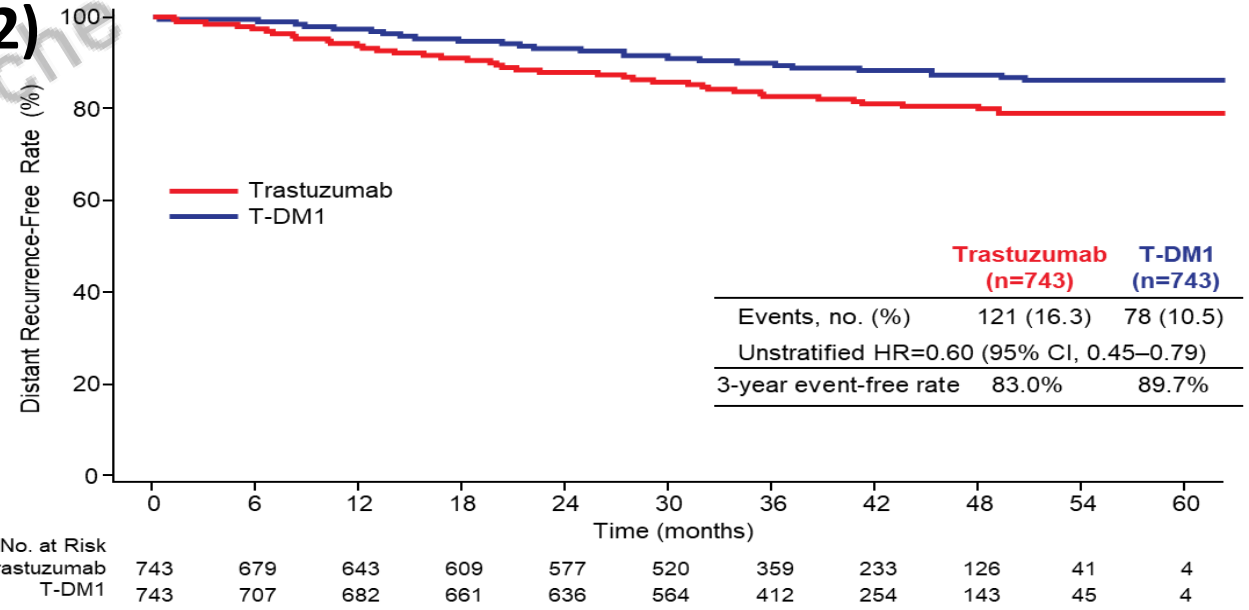
Geyer CE, et al. SABCS 2018; von Minckwitz G, et al. NEJM 2018

Invasive Disease-Free Survival (1) & distant recurrence (2)

(1)



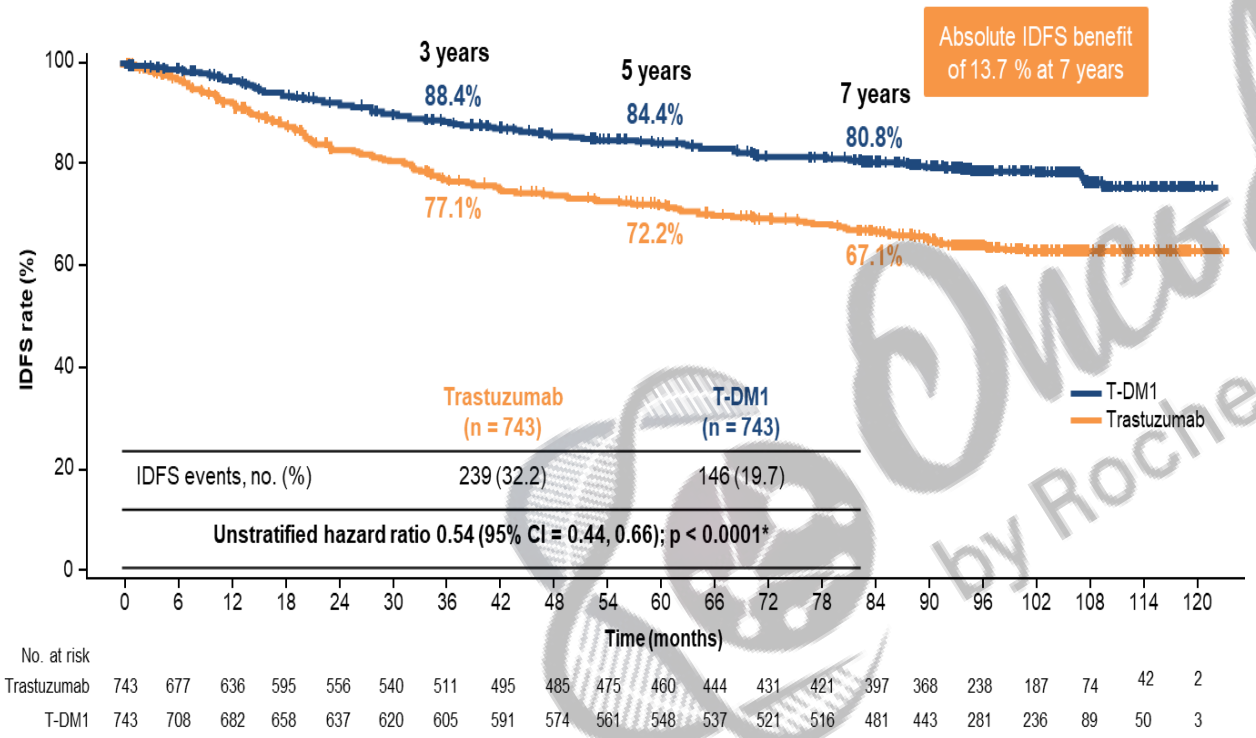
(2)



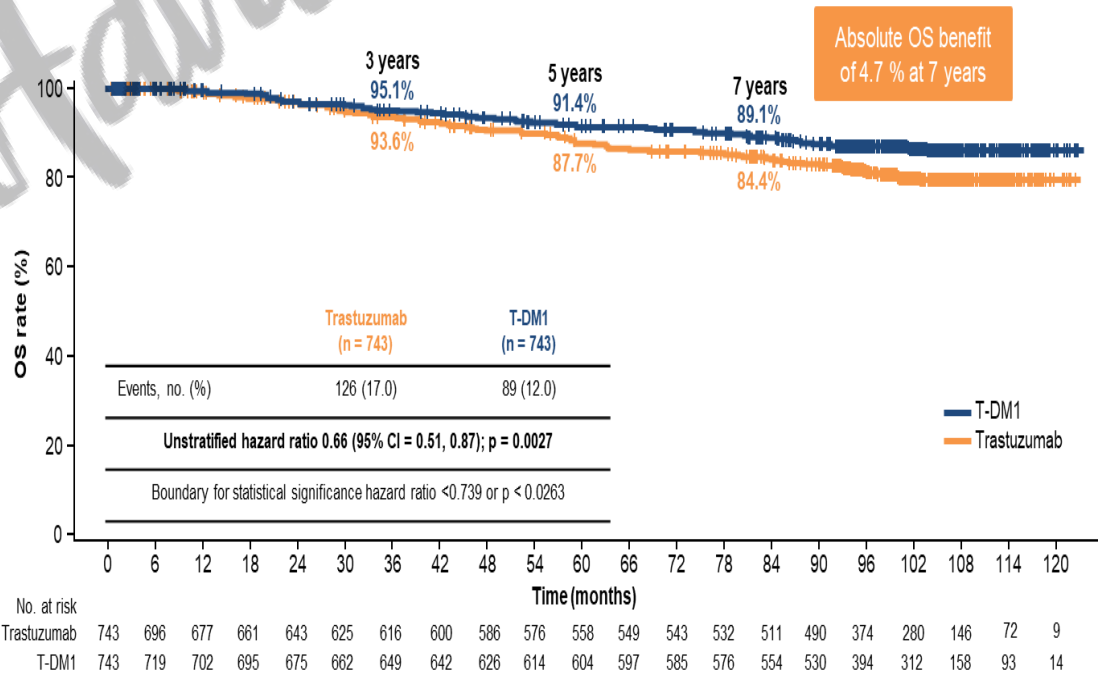
Geyer CE, et al. SABCS 2018; von Minckwitz G, et al. NEJM 2018

KATHERINE: Updated results

KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)



KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)



Loibl S, et al. SABCS 2023

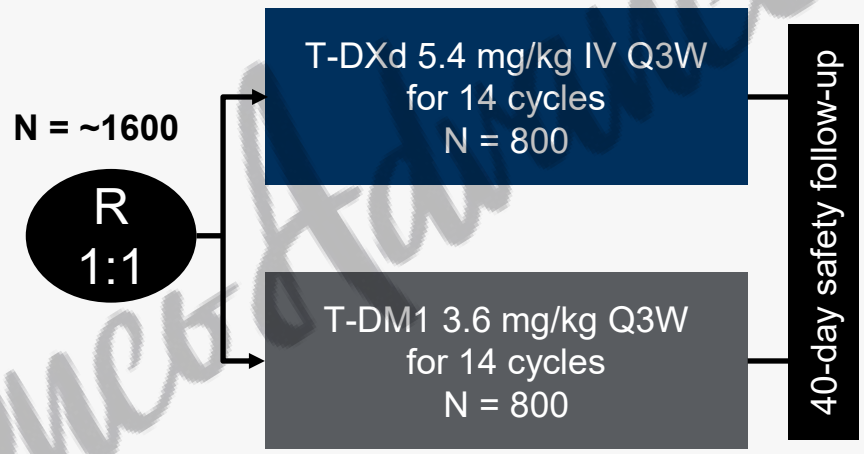
Destiny-Breast 05 Study design

A global, multicenter, randomized, open-label, phase 3 trial (NCT04622319)

Population

- Residual invasive disease in the breast and/or axillary lymph nodes after neoadjuvant chemotherapy and HER2-directed treatment[a]
- **High-risk**
  - **Inoperable eBC (cT4, N0-3, M0 or cT1-3, N2-3, M0) at presentation before NAT or**
  - **Operable eBC (cT1-3, N0-1, M0) with axillary node-positive disease (ypN1-3) after NAT**
- Centrally confirmed HER2+ (IHC 3+ or ISH+) eBC
- ECOG PS 0 or 1

Stratification factors
- Extent of disease status at presentation[b]
- HER2-targeted NAT (single, dual)
- Hormone receptor status (positive, negative)
- Post-NAT pathologic nodal status (positive [ypN1-3], negative [ypN0])



Primary endpoint
- IDFS

Key secondary endpoint
- DFS

Other secondary endpoints
- OS
- DRFI
- BMFI
- Safety

- **Concomitant adjuvant ET was allowed per local practices**
- **Adjuvant RT and ILD monitoring program:**
  - All patients receiving RT had chest CT scans prior to start of RT, 6 weeks after start of study treatment, then every 12 weeks while on treatment, and at 40-day follow-up
  - Patients completing RT prior to start of study medication (sequential) had an additional chest CT scan prior to start of study treatment

BMFI, brain metastasis–free interval; eBC, early breast cancer; DCO, data cutoff; DFS, disease-free survival; DRFI, distant recurrence–free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; IHC, immunohistochemistry; ISH, in situ hybridization; INV, investigator assessment; IV, intravenous; NAT, neoadjuvant therapy; OS, overall survival; Q3W, every 3 weeks; R, randomization; RT, radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]NAT is defined as ≥16 weeks NAT with ≥9 weeks trastuzumab ± pertuzumab and ≥9 weeks taxane-based chemotherapy. [b]Operable (cT1-3, N0, M0) vs inoperable (cT4, N0-3, M0 or cT1-3, N2-3, M0).

Geyer C, et al. ESMO 2025

Baseline demographics and clinical characteristics

	T-DXd n = 818	T-DM1 n = 817
Age, median (range), years	50.3 (24-78)	50.6 (21-83)
<65	735 (89.9)	736 (90.1)
≥65	83 (10.1)	81 (9.9)
Female sex, n (%)	814 (99.5)	814 (99.6)
Race		
White	301 (36.8)	333 (40.8)
Black or African American	22 (2.7)	13 (1.6)
Asian	399 (48.8)	386 (47.2)
Other	96 (11.7)	85 (10.4)
Region, n (%)		
Asia	392 (47.9)	380 (46.5)
Europe	222 (27.1)	223 (27.3)
North America + Australia	57 (7.0)	72 (8.8)
Rest of world[a]	147 (18.0)	142 (17.4)
ECOG PS score, n (%)		
0	656 (80.2)	652 (79.8)
1	162 (19.8)	165 (20.2)
HER2 expression,[b] n (%)		
IHC 3+	676 (82.6)	670 (82.0)
IHC 2+ and ISH+	129 (15.8)	133 (16.3)
IHC 2+ and ISH−	2 (0.2)	0
IHC 1+ and ISH+	11 (1.3)	14 (1.7)
Hormone receptor status,[c] n (%)		
Positive	581 (71.0)	583 (71.4)
Negative	237 (29.0)	234 (28.6)

	T-DXd n = 818	T-DM1 n = 817
Operative status at disease presentation,[c] n (%)		
Operable (cT1-3, N1, M0)	387 (47.3)	393 (48.1)
Inoperable (cT4, N0-3, M0 or cT1-3, N2-3, M0)	431 (52.7)	424 (51.9)
Post-NAT pathologic nodal status,[b] n (%)		
Positive	660 (80.7)	658 (80.5)
Negative	158 (19.3)	159 (19.5)
Neoadjuvant HER2-targeted therapy, n (%)		
Trastuzumab alone	176 (21.5)	171 (20.9)
Trastuzumab + pertuzumab	637 (77.9)	641 (78.5)
Trastuzumab + other HER2-targeted therapy	3 (0.4)	3 (0.4)
Trastuzumab + pertuzumab + other HER2-targeted therapy	2 (0.2)	2 (0.2)
Neoadjuvant chemotherapy, n (%)		
Taxanes	818 (100)	817 (100)
Platinum compounds	386 (47.2)	392 (48.0)
Anthracycline	423 (51.7)	399 (48.8)
Radiotherapy treatment, n (%)		
Adjuvant radiotherapy	764 (93.4)	759 (92.9)
Concurrent	438 (53.5)	480 (58.8)
Sequential	326 (39.9)	279 (34.1)
No radiotherapy	54 (6.6)	58 (7.1)

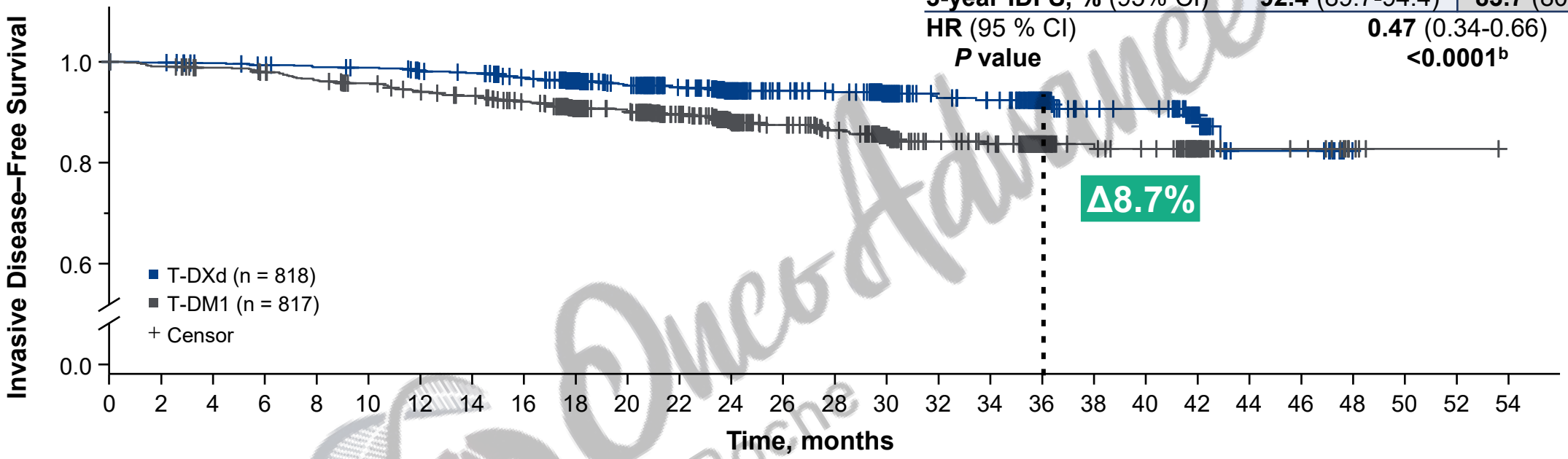
ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; NAT, neoadjuvant therapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Included regions: Argentina, Brazil, Chile, Czech Republic, Israel, Mexico, Peru, Poland, Romania, Russia. [b]Centrally confirmed. [c]As reported in electronic data capture.

Dr Charles E Geyer Jr

Geyer C, et al. ESMO 2025

Primary endpoint: IDFS[a]

	T-DXd n = 818	T-DM1 n = 817
Patients with events, n (%)	**51** (6.2)	**102** (12.5)
3-year IDFS, % (95% CI)	**92.4** (89.7-94.4)	**83.7** (80.2-86.7)
HR (95 % CI)	**0.47** (0.34-0.66)	
***P* value**	**<0.0001[b]**	



Number at Risk:

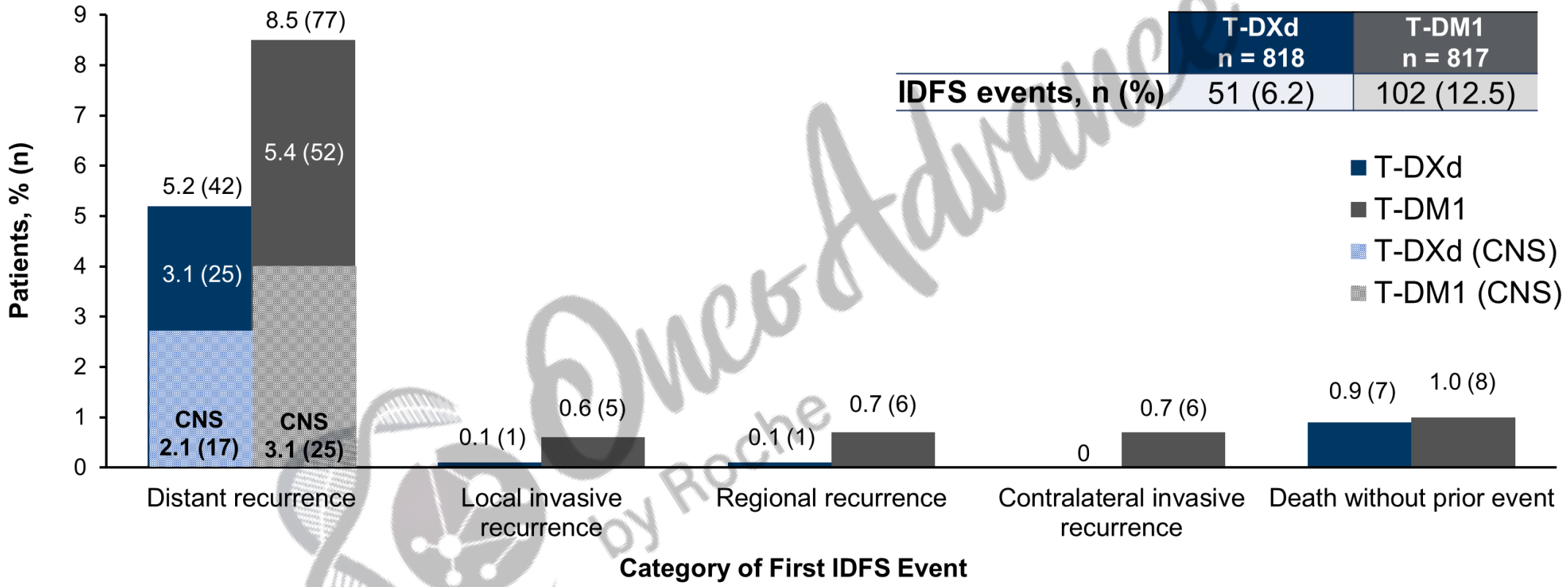
T-DXd	818	788	781	776	771	768	758	753	731	684	634	544	440	380	370	275	218	212	129	92	90	46	14	14	0	0	0	0
T-DM1	817	781	769	760	745	734	719	708	687	632	599	527	417	355	337	233	186	177	120	84	79	38	14	13	4	1	1	0

53% reduction in the risk of invasive disease recurrence or death for T-DXd compared with T-DM1

HR, hazard ratio; IDFS, invasive disease–free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Efficacy stopping boundary, *P* = 0.0183.
[a]IDFS is defined as the time from randomization until the date of first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. [b]Two-sided *P* value from stratified log-rank test. Hazard ratio and 95% CI from stratified Cox proportional hazards model with stratification factor of operative status at disease presentation.

Geyer C, et al. ESMO 2025

First IDFS event type



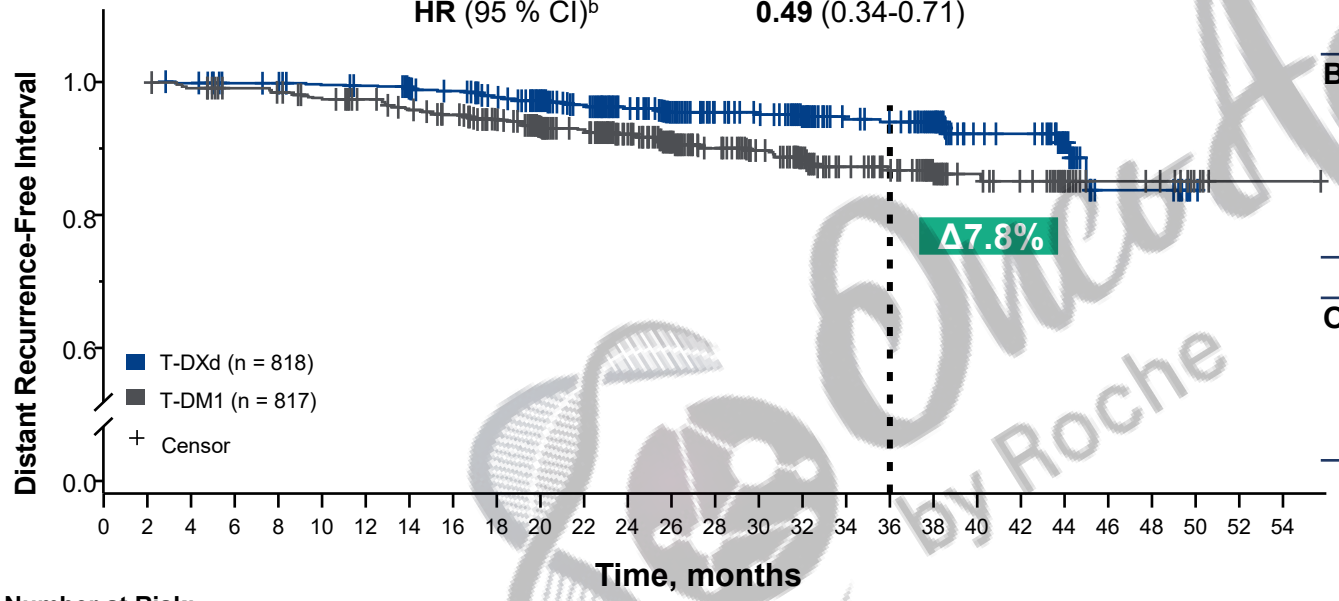
Lower rates of distant and locoregional recurrence were observed with T-DXd versus T-DM1

IDFS, invasive disease–free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Participants who experienced multiple types of IDFS events within 61 days of their first event are reported in the category according to the following hierarchy: distant recurrence CNS, distant recurrence non-CNS, local invasive recurrence, regional recurrence, contralateral breast cancer, and death without a previous event.

Geyer C, et al. ESMO 2025

Secondary endpoints: DRFI[a], BMFI, and OS

	T-DXd n = 818	T-DM1 n = 817
Patients with events, n (%)	**42** (5.1)	**81** (9.9)
3-year DRFI, % (95% CI)	**93.9** (91.4-95.7)	**86.1** (82.5-89.1)
HR (95 % CI)[b]	**0.49** (0.34-0.71)	



Number at Risk:

T-DXd	818	786	778	774	770	767	757	753	731	684	635	545	442	382	372	276	219	213	129	92	90	46	14	14	0	0	0	0
T-DM1	817	780	769	761	746	739	724	713	694	639	606	533	424	362	345	240	192	182	121	84	79	38	14	13	4	1	1	0

	T-DXd n = 818	T-DM1 n = 817
BMFI		
Patients with recurrence in CNS, n (%)	**17** (2.1)	**26** (3.2)
3-year BMFI rate, % (95% CI)	**97.6** (96.2-98.5)	**95.8** (93.6-97.2)
HR (95% CI)[b]	**0.64** (0.35-1.17)	
OS (2.9% maturity)		
Patient deaths, n (%)	**18** (2.2)	**29** (3.5)
Survival at 3 years % (95% CI)	**97.4** (95.8-98.4)	**95.7** (93.5-97.2)
HR (95% CI)[b]	**0.61** (0.34-1.10)	

BMFI, brain metastasis–free interval; DRFI, distant recurrence–free interval; HR, hazard ratio; OS, overall survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]DRFI is defined as the time between randomization and the date of distant breast cancer recurrence. [b]HR and 95% CI from stratified Cox proportional hazards model with stratification factor of operative status at disease presentation.

Geyer C, et al. ESMO 2025

Overall safety summary

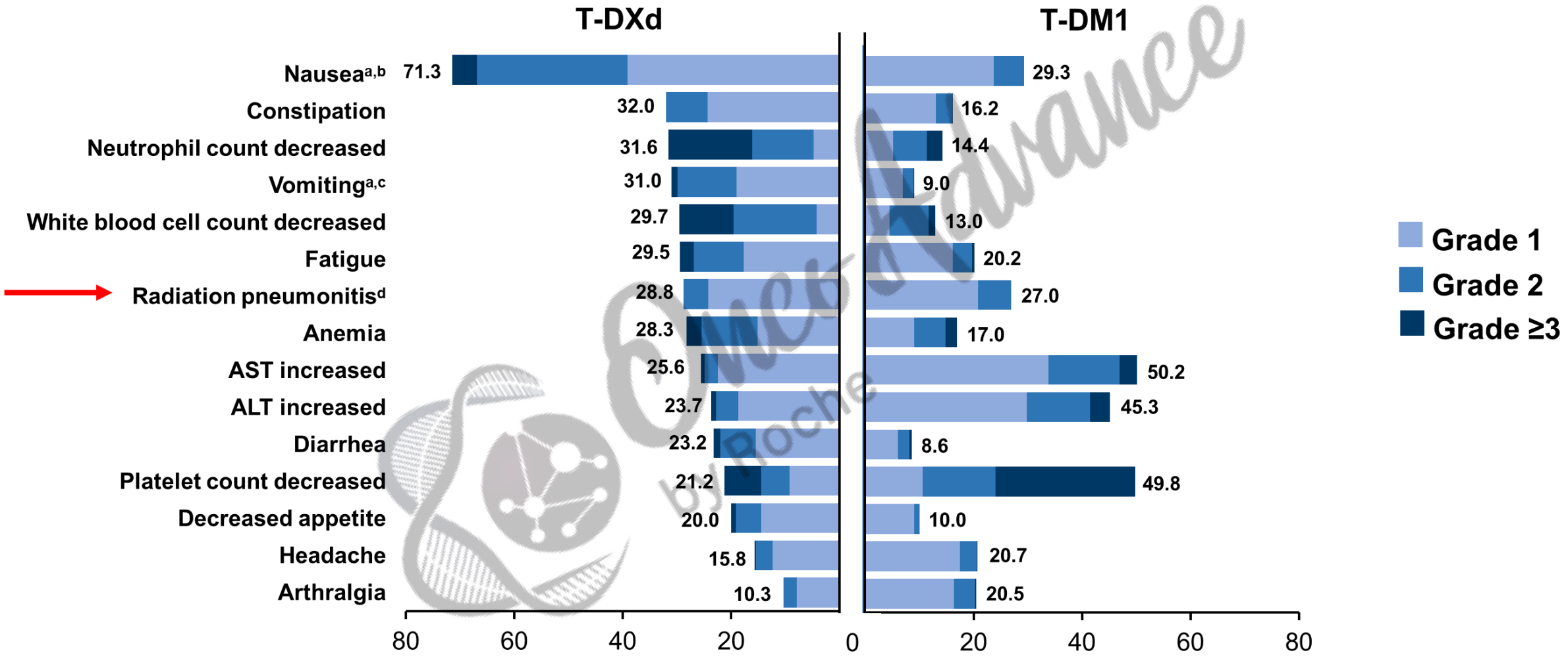
TEAEs, n (%)	T-DXd n = 806[a]	T-DM1 n = 801[a]
Any grade	802 (99.5)	788 (98.4)
Grade ≥3	**408 (50.6)**	**416 (51.9)**
Serious	**140 (17.4)**	**109 (13.6)**
Associated with drug discontinuation	**144 (17.9)**	**103 (12.9)**
Drug-related ILD/pneumonitis[b]	**87 (10.8)**	**20 (2.5)**
Associated with drug interruptions	400 (49.6)	329 (41.1)
Associated with dose reductions	**213 (26.4)**	**213 (26.6)**
Associated with deaths	**3 (0.4)**	**5 (0.6)**

- **In the T-DXd arm, causes of death (n = 3) were 2 ILD/pneumonitis[c] and respiratory tract infection (adjudicated as not ILD)**
- **In the T-DM1 arm, causes of death (n = 5) were leiomyosarcoma of the uterus, aneurysm, non-neutropenic sepsis, ovarian cancer, and traumatic pneumothorax**

ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-related adverse event.
[a]All patients who received at least 1 dose of study treatment. [b]Investigator-assessed as drug-related ILD and pneumonitis per preferred term. [c]Investigator assessed and adjudication committee confirmed.

Geyer C, et al. ESMO 2025

TEAEs in ≥20% of patients (either arm)



ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]Prophylactic antiemetics were recommended but not mandatory. [b]In the T-DXd and T-DM1 arms: 39.1% and 23.7% grade 1, 27.8% and 5.5% grade 2, and 4.5% and 0.1% grade 3 events, respectively. [c]In the T-DXd and T-DM1 arms: 19.0% and 6.9% grade 1, 10.9% and 2.0% grade 2, and 1.1% and 0.1% grade 3 events. [d]In the T-DXd and T-DM1 arms: 24.2% and 20.8% grade 1, 4.6% and 6.1% grade 2 events.

Geyer C, et al. ESMO 2025

Adverse events of special interest: ILD/pneumonitis and LV dysfunction

n (%)	Adjudicated Drug-related ILD					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
T-DXd (n = 806)[a]	77 (9.6)	16 (2.0)	52 (6.5)	7 (0.9)	0	2 (0.2)
T-DM1 (n = 801)[a]	13 (1.6)	8 (1.0)	5 (0.6)	0	0	0

Adjuvant radiotherapy timing (sequential or concurrent) showed no differences in adjudicated drug-related ILD

Similar distributions of any grade adjudicated drug-related ILD events were observed with sequential and concurrent radiotherapy in both treatment arms (T-DXd: 10.7% and 9.6.% vs T-DM1: 2.6% and 1.0%, respectively)

n (%)	LV dysfunction					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
T-DXd (n = 806)[a]	23 (2.9)	1 (0.1)	20 (2.5)	2 (0.2)	0	0
T-DM1 (n = 801)[a]	14 (1.7)	0	11 (1.4)	3 (0.4)	0	0

CT, computed tomography; ILD, interstitial lung disease; LV, left ventricular; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]All patients who received at least 1 dose of study treatment.

Geyer C, et al. ESMO 2025

Eligibility criteria for DESTINY-Breast05 differed from those in the KATHERINE study[1,2]

DESTINY-Breast05 enrolled a higher-risk population than KATHERINE, as patients with operable BC and N0 RD after neoadjuvant therapy were ineligible, but were permitted in KATHERINE

Key eligibility criteria	DESTINY-Breast05[1]	KATHERINE[2]
Response to prior neoadjuvant therapy	RD in breast and/or axillary lymph nodes after neoadjuvant chemotherapy + HER2-targeted therapy	RD in breast or axillary lymph nodes after neoadjuvant taxane + trastuzumab-based therapy
Disease at presentation	• Inoperable BC (cT4, N0–3, M0 or cT1–3, N2–3, M0), OR • Operable BC (cT1–3, N0–1, M0) **with axillary N+ disease (ypN1–3) after neoadjuvant therapy**	cT1–4, N0–3, M0 (excluding T1a/b N0)
Patient characteristics		
N0 after neoadjuvant therapy	19%	**46%**
Inoperable disease at baseline	**52%**	25%
Received prior neoadjuvant PH	78%	18%
Received prior anthracyclines	50%	77%
Asian patients*	47%	9%

In DB-05 study, 78% patients received neoadjuvant PH

Cross-trial comparisons should be interpreted with caution due to differences in study designs and patient populations.

* HCP insights suggest the imbalance of Asian patients is unlikely to impact extrapolation of the results to clinical practice.

BC, breast cancer; H, trastuzumab; HCP, healthcare professional; P, pertuzumab; RD, residual invasive disease.

1. Geyer Jr CE, *et al.* ESMO 2025 (Oral LBA1); 2. von Minckwitz G, *et al. N Engl J Med* 2019; **380:**617–628.

Perspectives on DESTINY-Breast05

Practice changing! But … for whom?

Careful balancing of benefit against safety risk is required in this curative setting

Advantages of using T-DXd

- Reduces risk of recurrence by half vs. T-DM1[1]
- Benefit seen across all subgroups[1]
- May reduce risk of CNS recurrence[1]
- Similar treatment duration and proportion of patients completing 14 cycles[1]
- Similar rate of radiation pneumonitis as T-DM1[1]

Disadvantages of using T-DXd

- ~10% ILD rate and two ILD-related deaths[1]
- Cost burden of frequent CT monitoring of ILD[2]
- Higher incidence of serious TEAEs and TEAEs associated with drug interruption/discontinuation[1]
- Unknown impact on QoL/PROs[2]
- Unknown OS benefit[1,2] (vs. 34% reduction in risk of death with T-DM1 vs. H in KATHERINE[3])

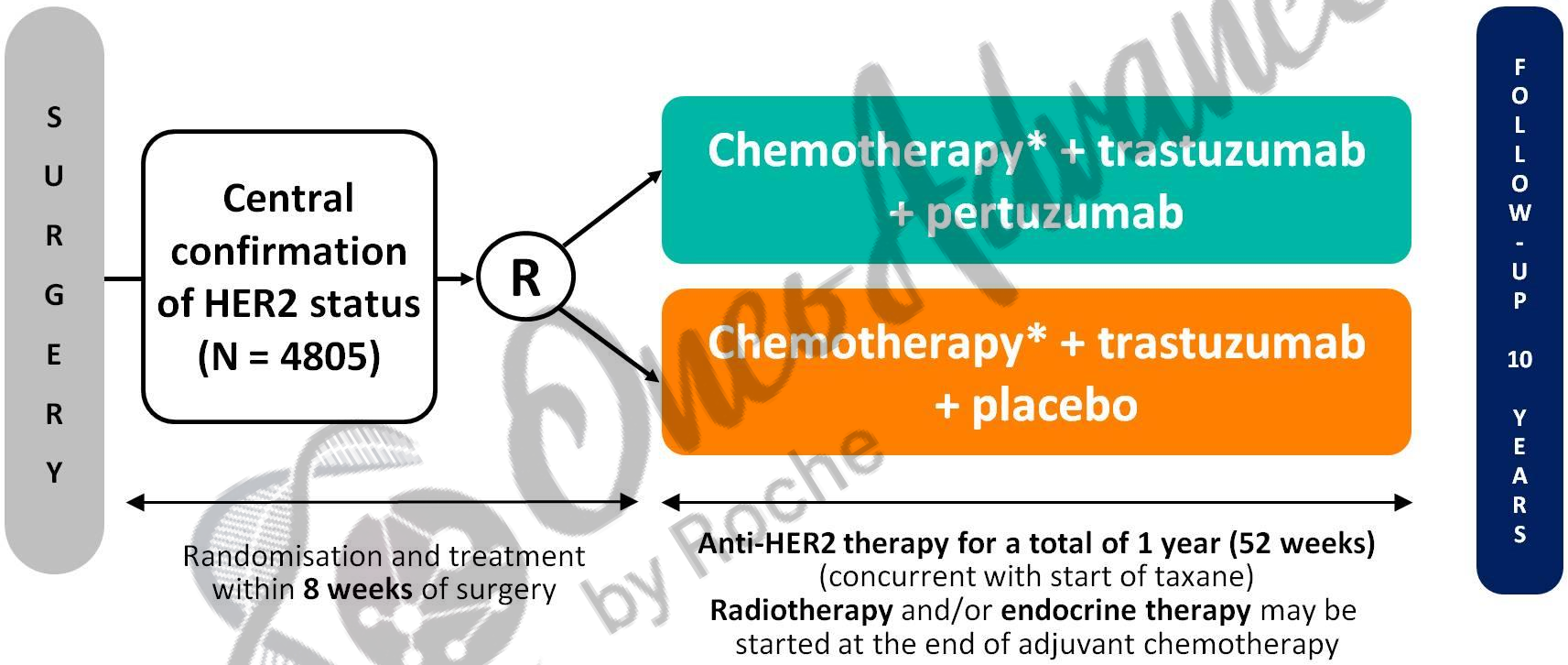
- There will likely be two SoC escalation strategies for patients with HER2+ eBC and RD after neoadjuvant therapy:[2]
  - T-DM1 for patients with operable disease at baseline or RD N0
  - T-DXd for selected high-risk patients with inoperable disease at baseline or if operable, RD N+ (meeting the DESTINY-Breast05 eligibility criteria[1])

CNS, central nervous system; CT, computed tomography; eBC, early breast cancer; H, trastuzumab; ILD, interstitial lung disease; OS, overall survival; PRO, patient-reported outcome; QoL, quality of life; RD, residual invasive disease; SoC, standard-of-care; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

1. Geyer Jr CE, *et al.* ESMO 2025 (Oral LBA1); 2. Tolaney SM. ESMO 2025 (Discussant for LBA1); 3. Geyer Jr CE, *et al. N Engl J Med* 2025; **392:**249–257.

APHINITY Study

APHINITY: Trial Design



*A number of standard anthracycline-taxane-sequences or a non-anthracycline (TCH) regimen were allowed

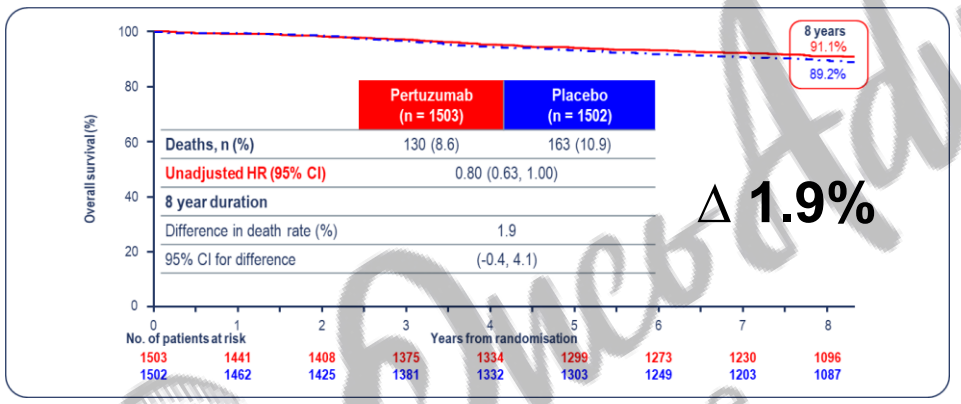
BIG
Breast International Group

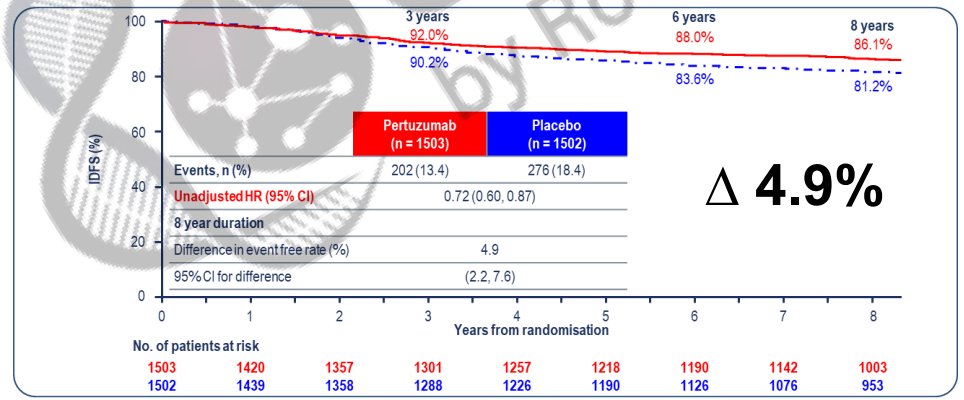
Von Minckwitz G, et al. ASCO 2017

Updated results of APHINITY at 8.4 years median follow up

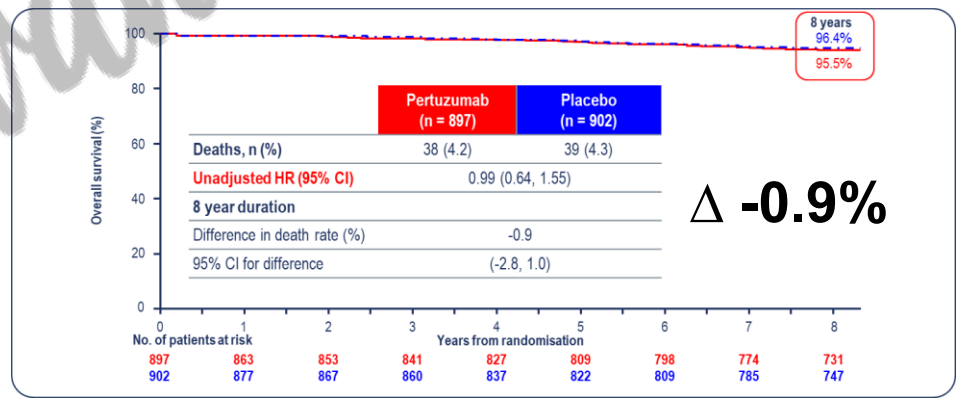
3rd interim OS analysis CCOD: Jan 10 2022

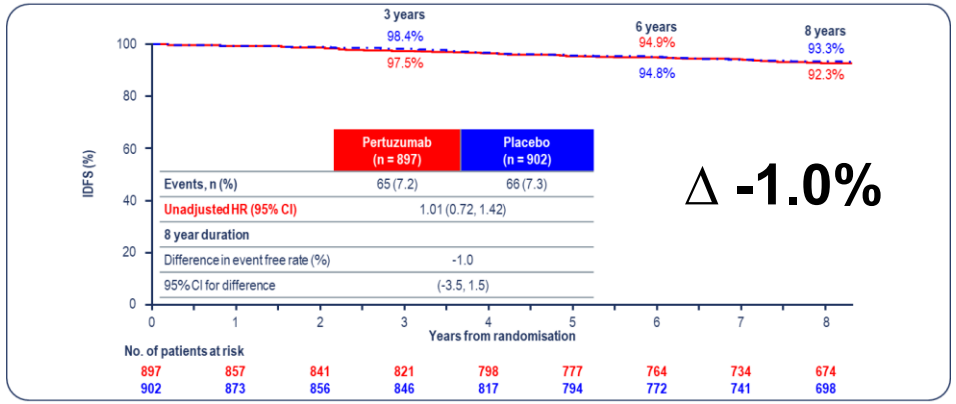
Node positive





Node negative



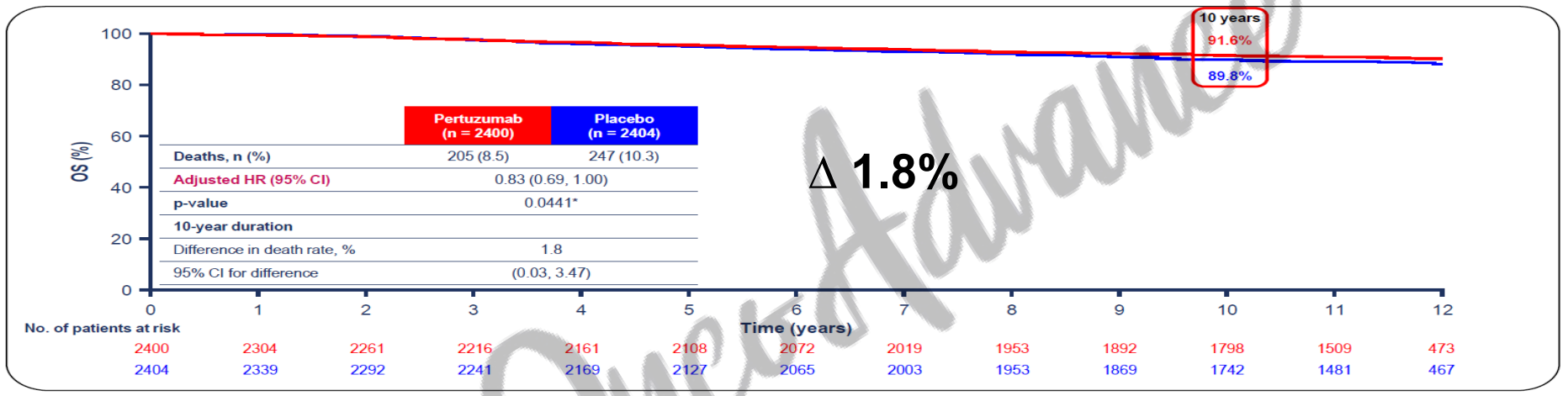


Updated Descriptive IDFS Analysis by Treatment Regimen

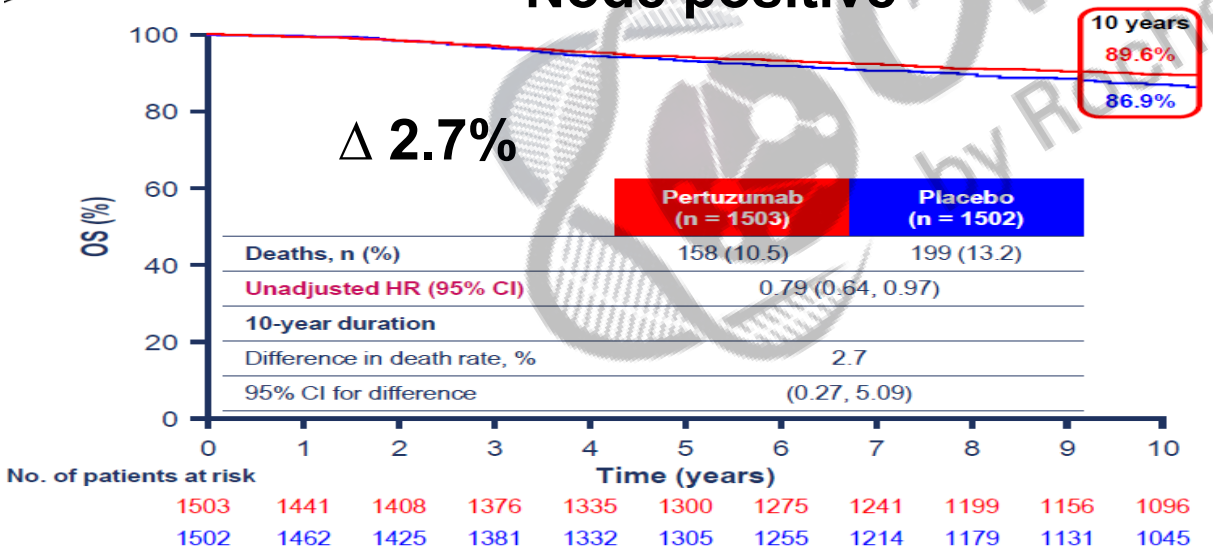
Loibl S, et al. ESMO Virtual Plenary 2022

Updated results of APHINITY at 11.3 years median follow up (Final OS)

ITT



Node positive



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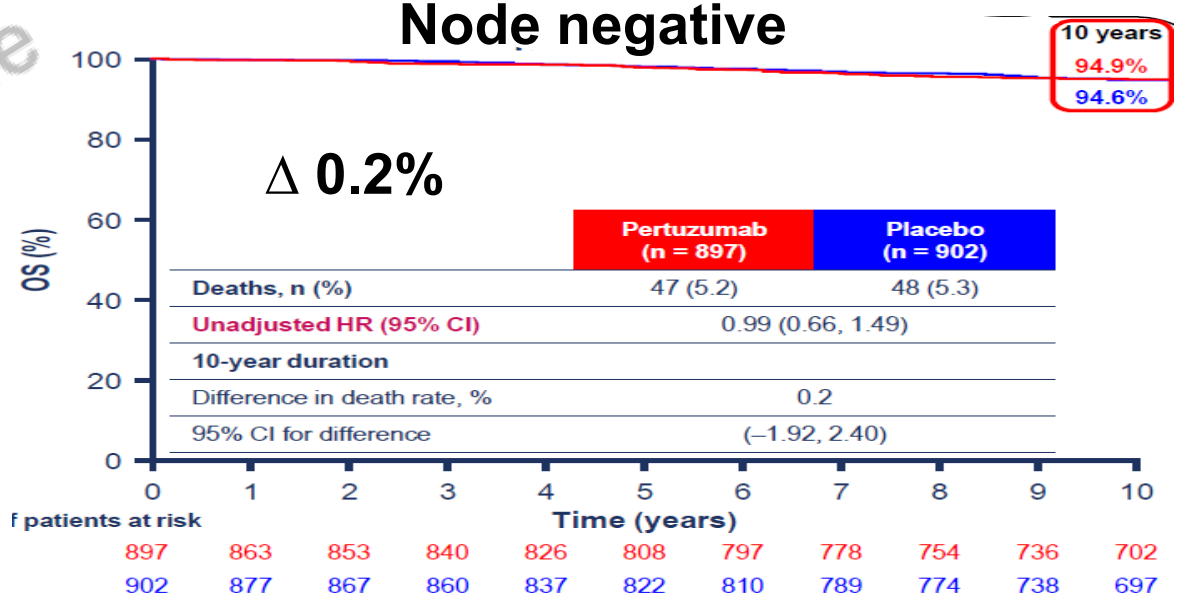
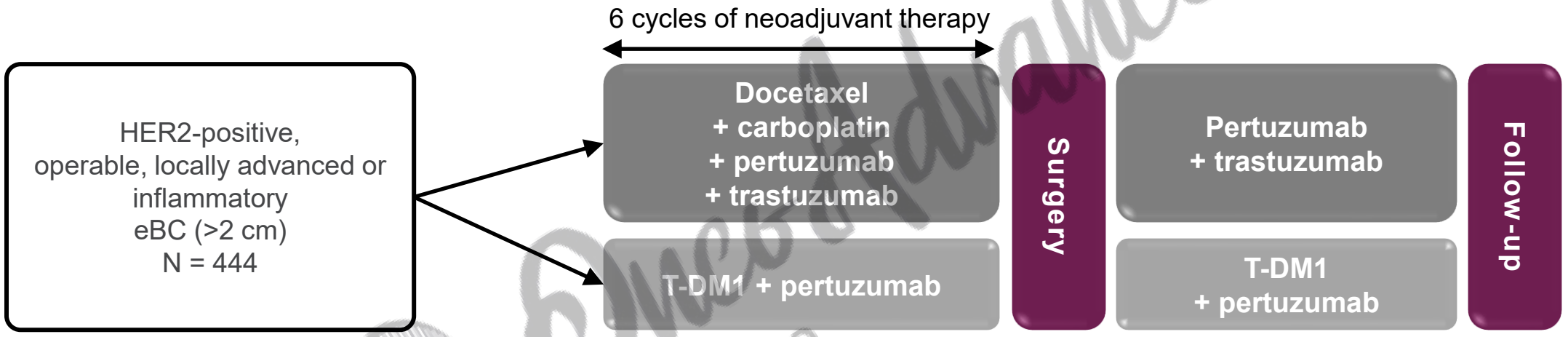


Loibl S, et al. ESMO Breast 2025

Can we de-escalate treatment into the routine practice in the neoadjuvant setting?

Can we de-escalate chemotherapy?

KRISTINE: pCR rates after neoadjuvant T-DM1 + P vs. TCHP

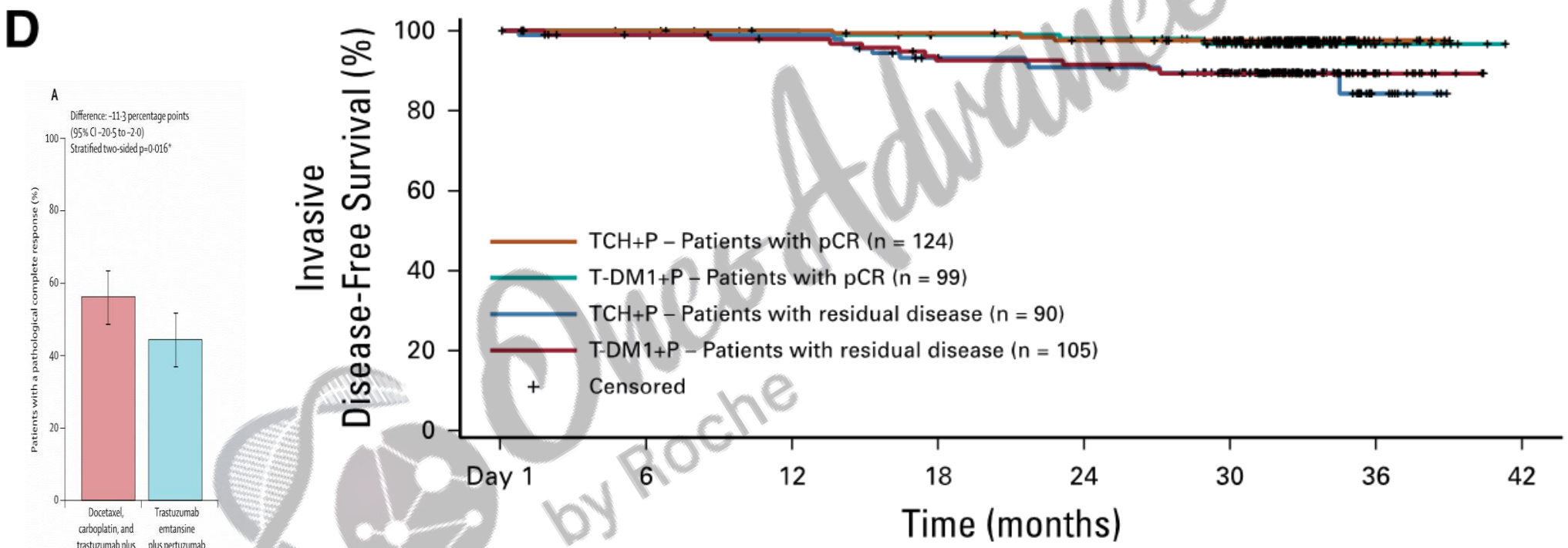


ITT population	TCHP (n = 221)	KP (n = 223)	p-value
pCR rate			
Overall, % (95% CI)	55.7 (48.8–62.3)	44.4 (37.8–51.2)	0.0155
ER+, %	43.8	35.1	
ER–, %	73.2	54.2	

Hurvitz S, et al. ASCO 2016

Can we de-escalate chemotherapy?

KRISTINE: iDFS depending on pCR after neoadjuvant T-DM1 + P vs. TCHP



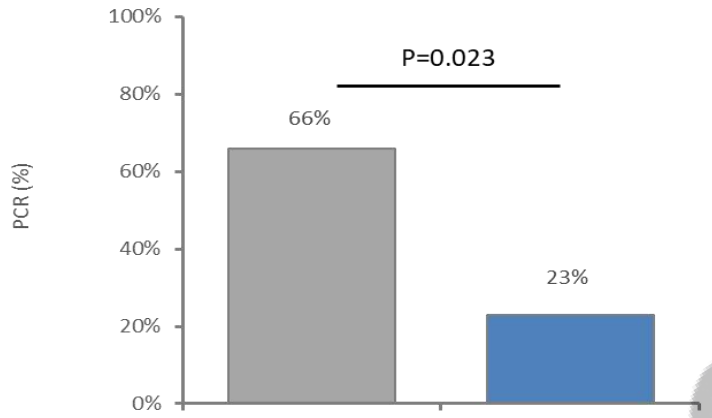
Additional chemotherapy: none in TCH+P arm
T-DM1+P: 41/124 [33.1%] with non-pCR; 9/99 [9.1%] with pCR)

Hurvitz et al, Lancet Oncology 2018 and JCO 2020

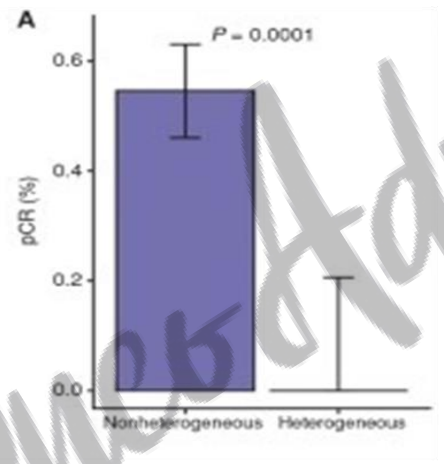
Do we have biomarkers for clinical practice?

Many biomarkers based on retrospective analysis…

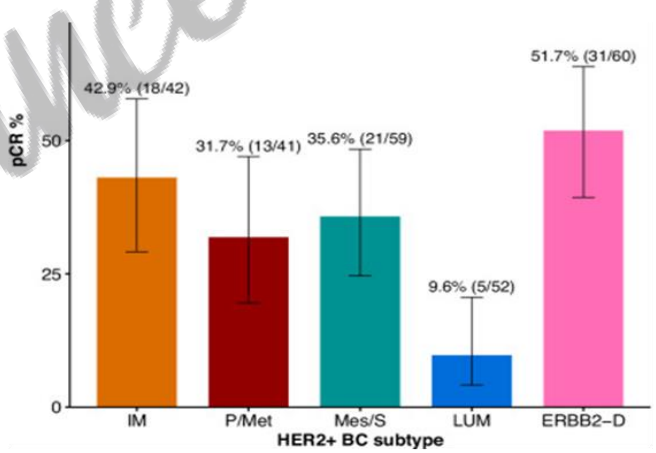
HER2 3+ vs. HER2 2+/ISH+



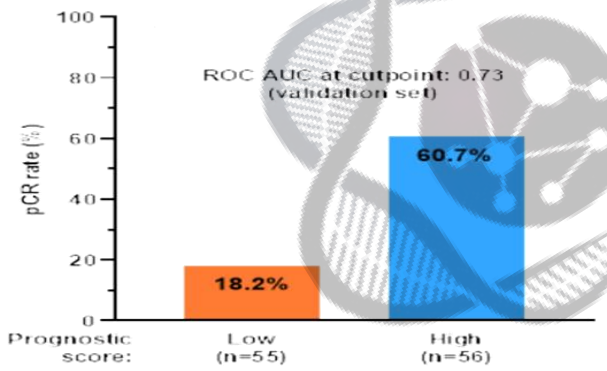
Intratumoral heterogeneity (ITH)



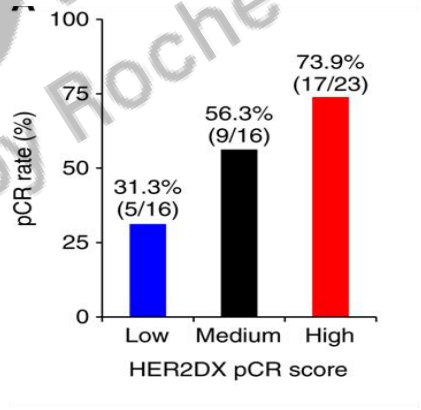
HER2 molecular subtypes



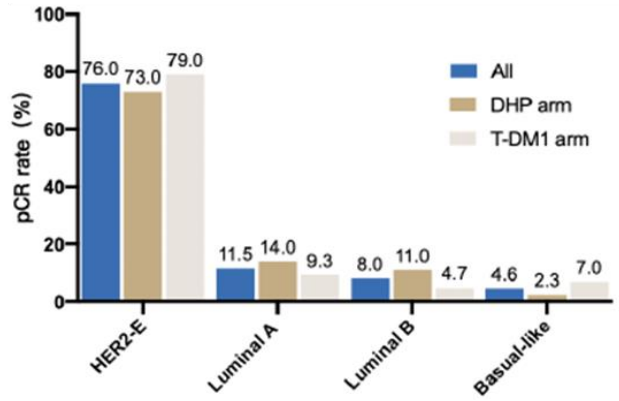
WSG ADAPT prognostic score



HER2DX PCR score



PAM50

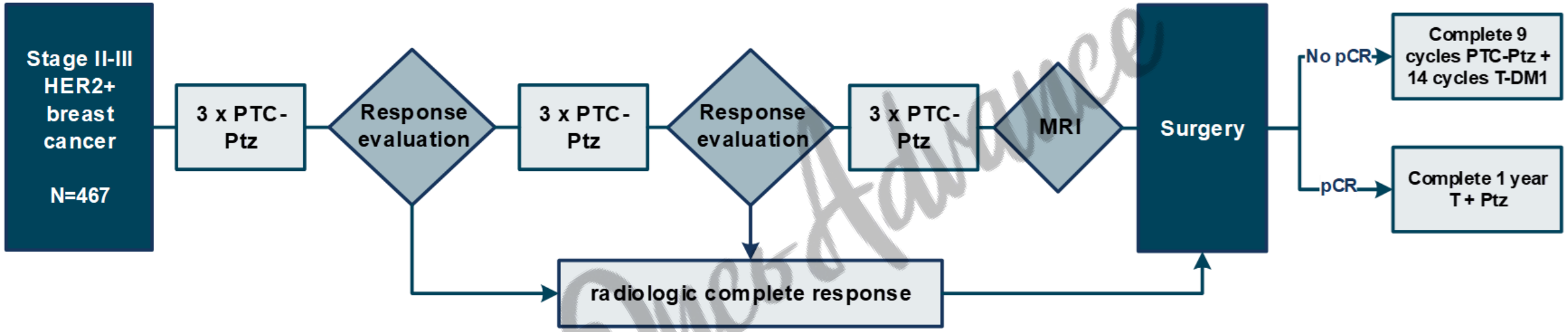


Sonke G. SABCS 2024

Pérez-García. ASCO 2024; Pérez-García. Lancet 2024; Metzger-Filho. Cancer Discovery 2021; Llombart-Cussac Clin Cancer Res. 2024; Redit. Nat Commun 2024; Aranzaru. JAMA Oncol. 2024; Graeser. SABCS 2023

Optimizing therapy based on individual activity…
De-escalating chemotherapy…

TRAIN-3: treatment duration based on MRI



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/m^2 i.v.; C = carboplatin AUC 6 mg•ml/min i.v.;
T = trastuzumab 6 mg/kg i.v.; Ptz = pertuzumab 420 mg i.v.

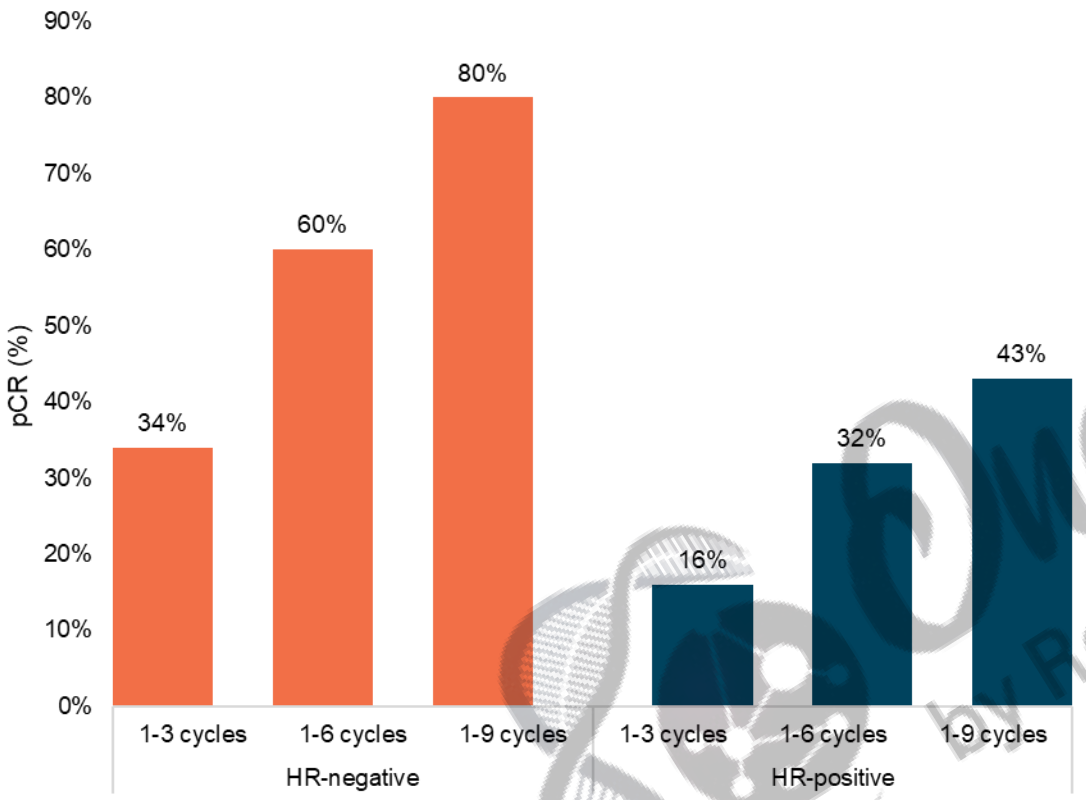
Radiological complete response (rCR): complete remission on MRI breast & axillary ultrasound combined with negative FNA/core biopsy in baseline N+ & negative vacuum assisted core biopsies of the marked original tumor region in HR+ patients

A 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.

ClinicalTrials.gov ID: NCT03820063

Van de Voort et al. Lancet Oncol 2024

TRAIN-3: treatment duration based on MRI

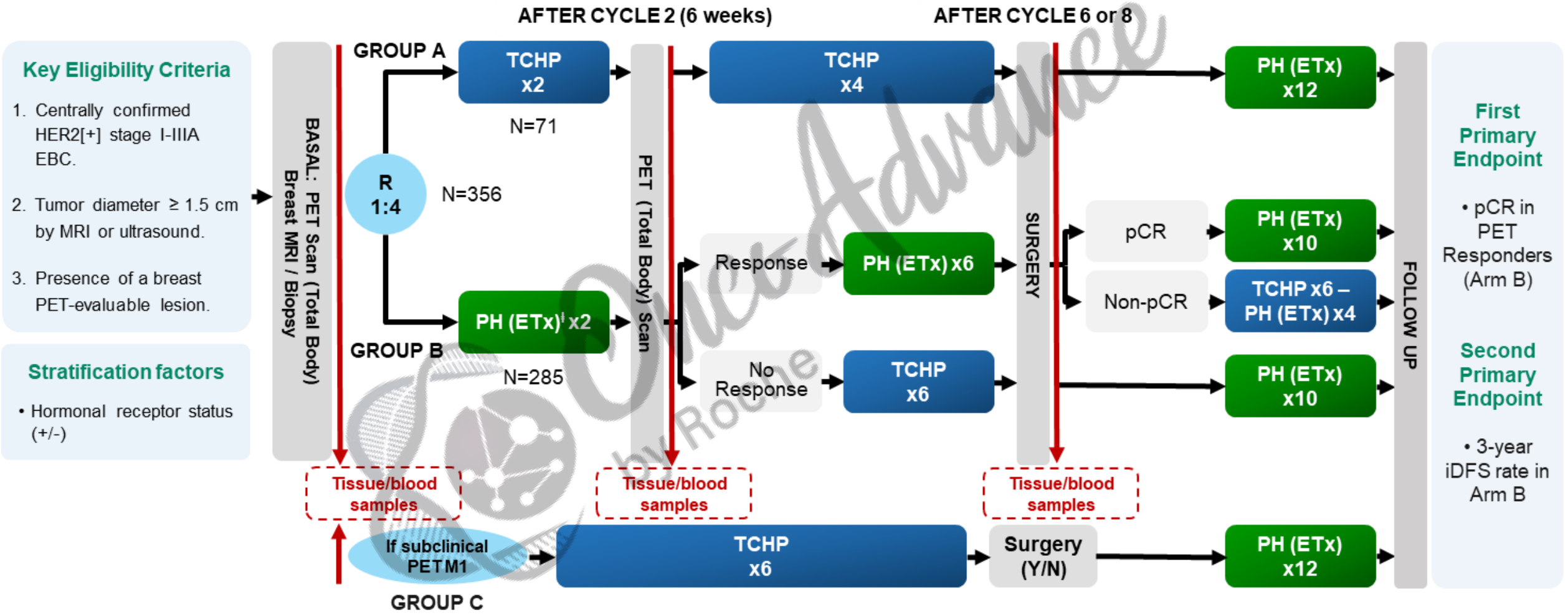


MRI accuracy (NPV) to predict a pCR:
HR-negative = 87%; HR-positive 53%

- **1 in 3 patients HER2+/ER- achieves pCR after 3 cycles**
- **MRI identifies these patients with 87% accuracy**
- **Better monitoring tools needed in HER2+/HR+**
- **3-year EFS data will be presented Wednesday (RF1-03)**

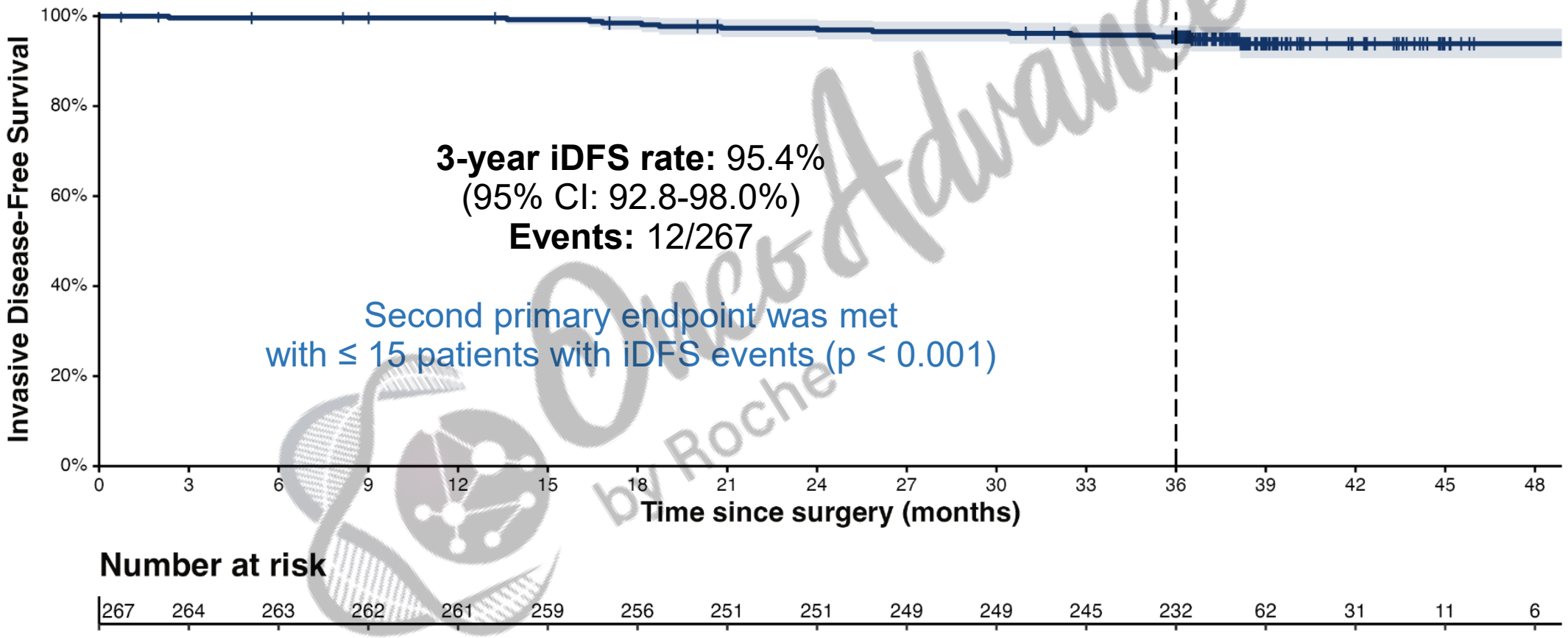
Van de Voort et al. Lancet Oncol 2024

PHERGain study design



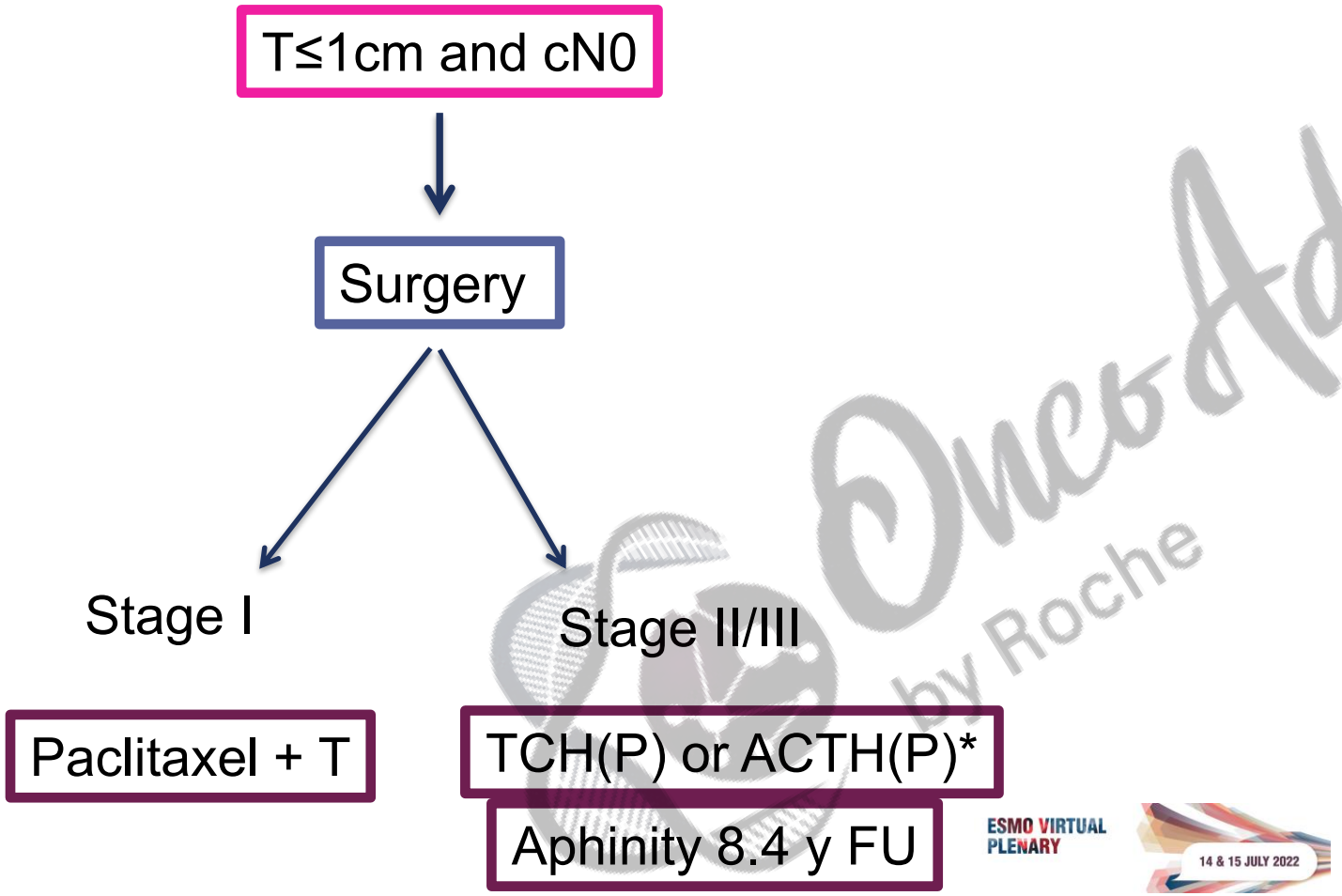
Cortes J, et al. ASCO 2023; Perez-Gracia J, et al. Lancet 2024 (in press)

Second Primary: iDFS (Arm B)



Cortes J, et al. ASCO 2023; Perez-Gracia J, et al. Lancet 2024 (in press)

HER2+ EBC management algorithm



ESMO VIRTUAL PLENARY 14 & 15 JULY 2022

*Depending on Nodal Status (consider biomarkers)
pT1apN0: paclitaxel + trastuzumab in HR-; for HR+, discuss case by case
pT1bcpN0: paclitaxel + trastuzumab

HER2+ EBC management algorithm

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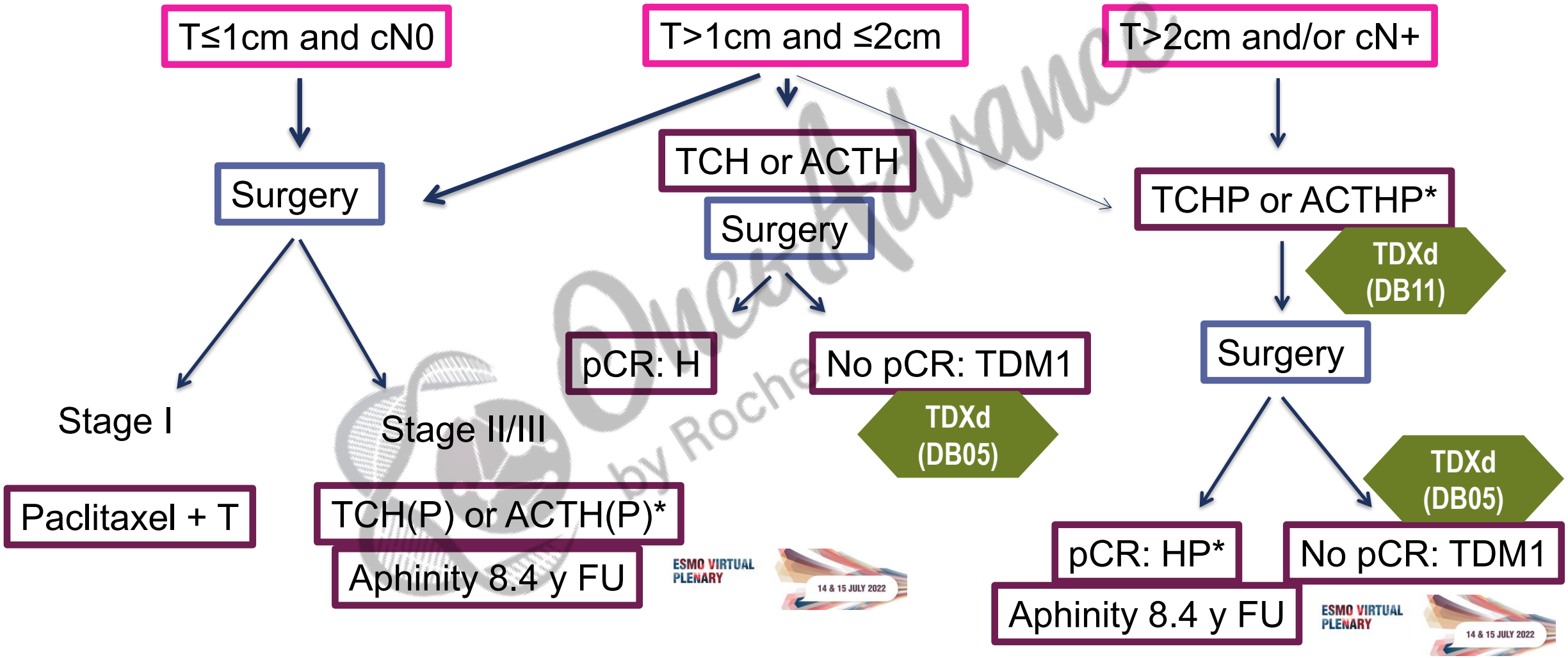

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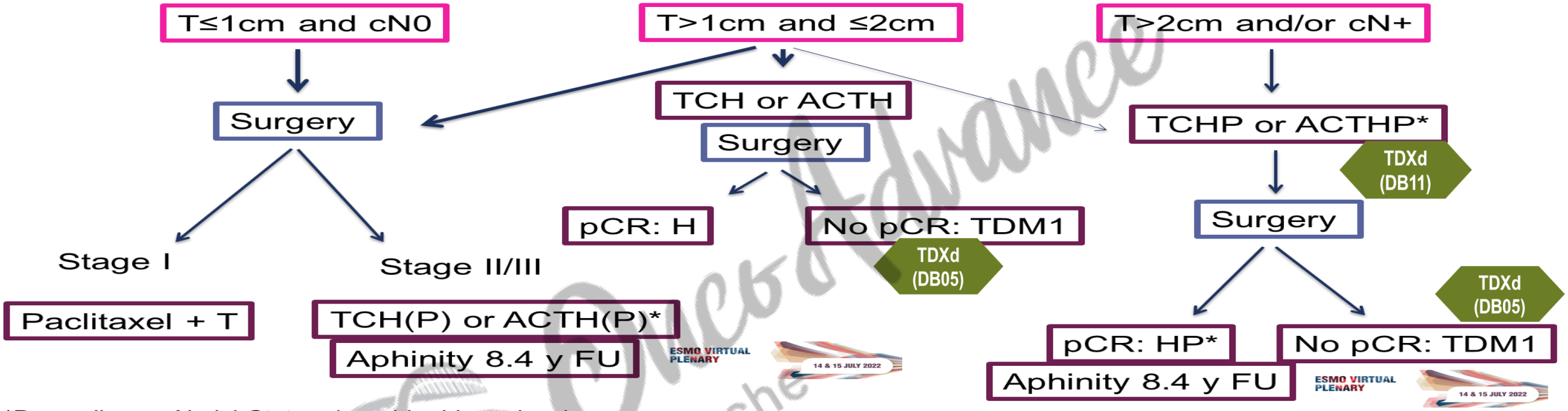


*Depending on Nodal Status (consider biomarkers)
pT1apN0: paclitaxel + trastuzumab in HR-; for HR+, discuss case by case
pT1bcpN0: paclitaxel + trastuzumab

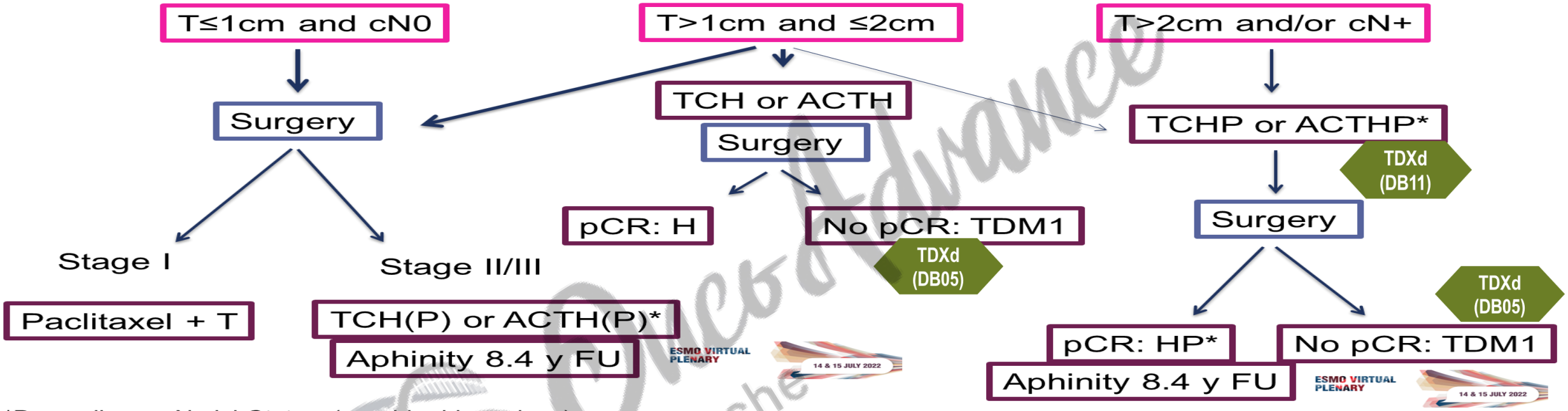
PHERGAIN Strategy

Each patient →

Biomarkers

← Each tumor

HER2+ EBC management algorithm



*Depending on Nodal Status (consider biomarkers)
pT1apN0: paclitaxel + trastuzumab in HR-; for HR+, discuss case by case
pT1bcpN0: paclitaxel + trastuzumab

PHERGAIN Strategy

Each patient → **BEST STRATEGY** ← Each tumor

Biomarkers