(Neo)-Adjuvant systemic therapy in patients with early HER2 positive breast cancer

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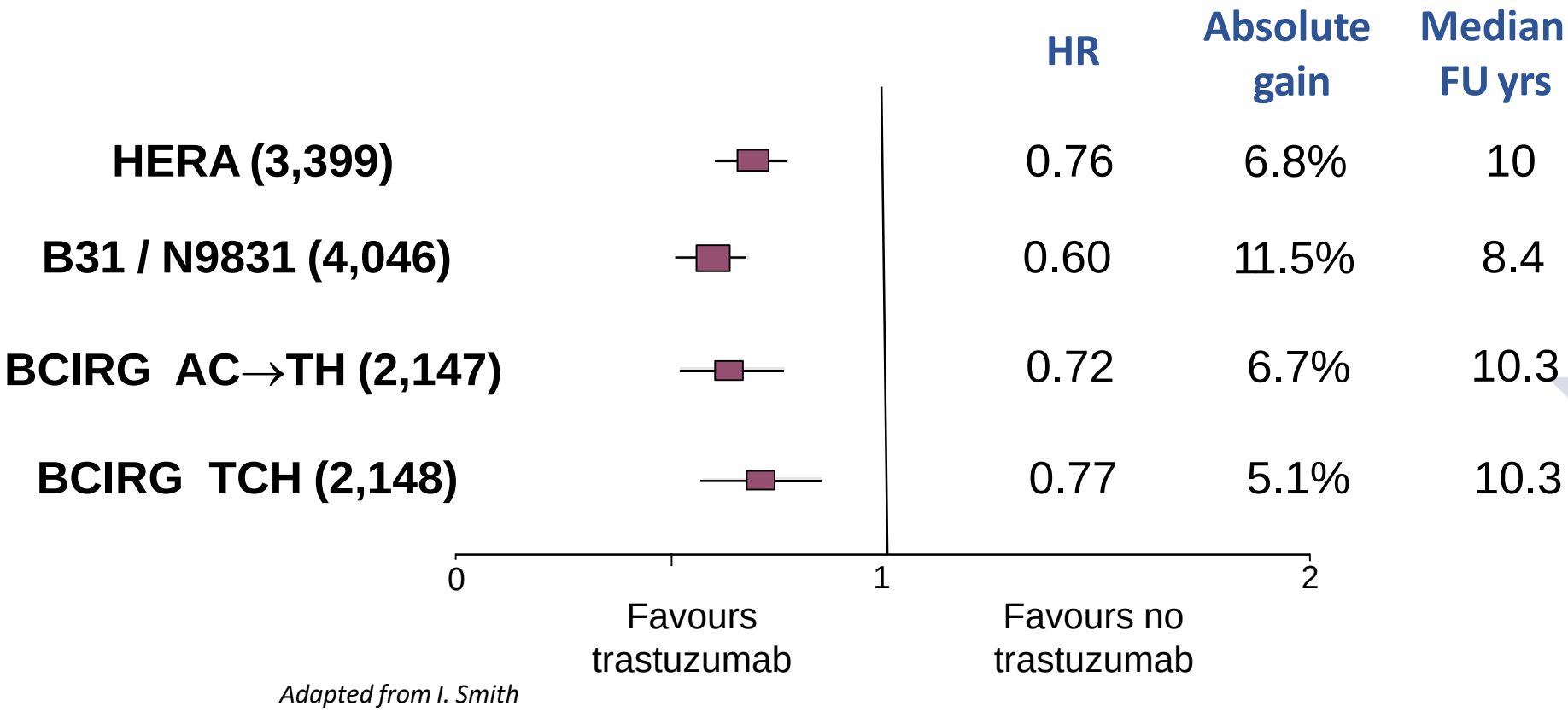
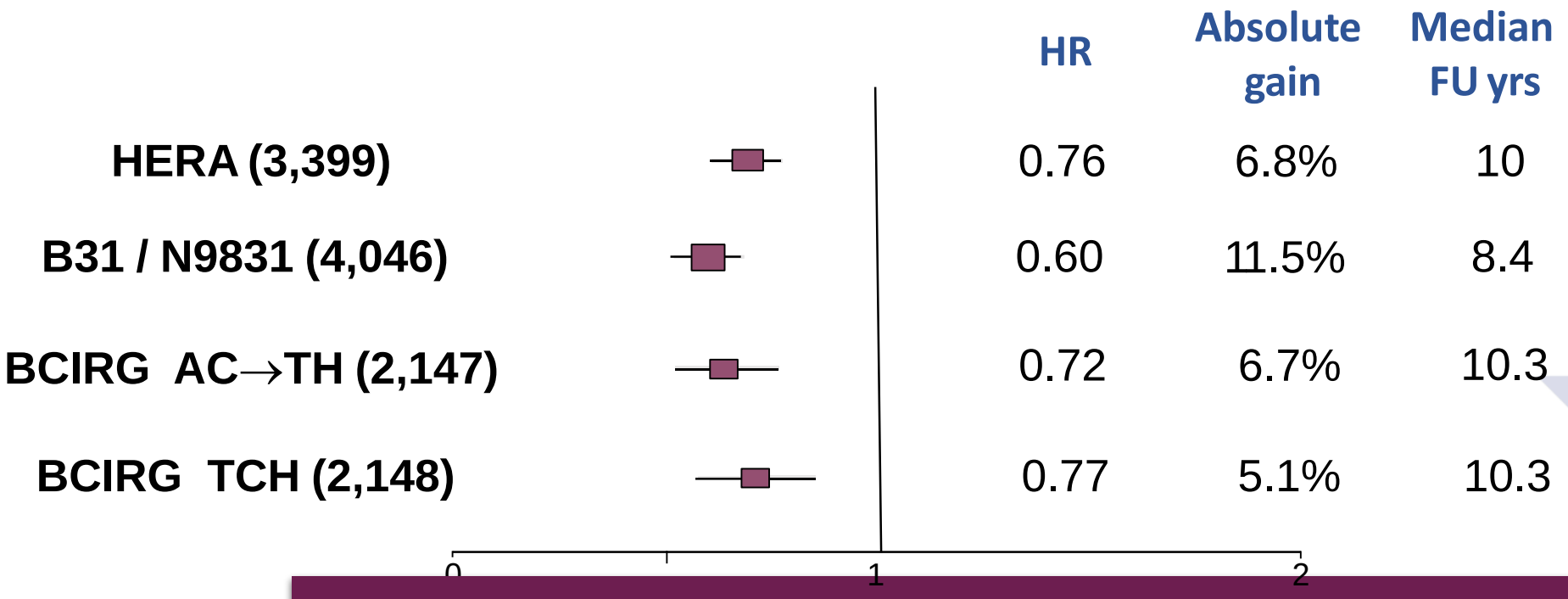
Early HER2 positive

1 year adjuvant Trastuzumab improves DFS compared to no Trastuzumab



Adapted from I. Smith

1 year adjuvant Trastuzumab improves DFS compared to no Trastuzumab



Improvement in OS as well

DE-ESCALATION ATTEMPTS BY SHORTENING THE DURATION OF ADJUVANT TRASTUZUMAB

Trial	Number of patients	Prespecified non-inferiority margin	Results
6 months vs. 12 months			
PHARE[1]	3380	1.15	HR 1.28 (95% CI, 1.05-1.56)
HORG[2]	481	1.53	HR 1.57 (95% CI, 0.86-2.10)
PERSEPHONE[3]	4089	1.31	**HR 1.07 (95% CI, 0.93-1.24)**
9 weeks vs. 12 months			
Short-HER[4]	1253	1.29	HR 1.15 (90% CI, 0.91-1.46)
SOLD[5]	2174	1.3	HR 1.39 (90% CI, 1.12-1.72)

11377 patients!

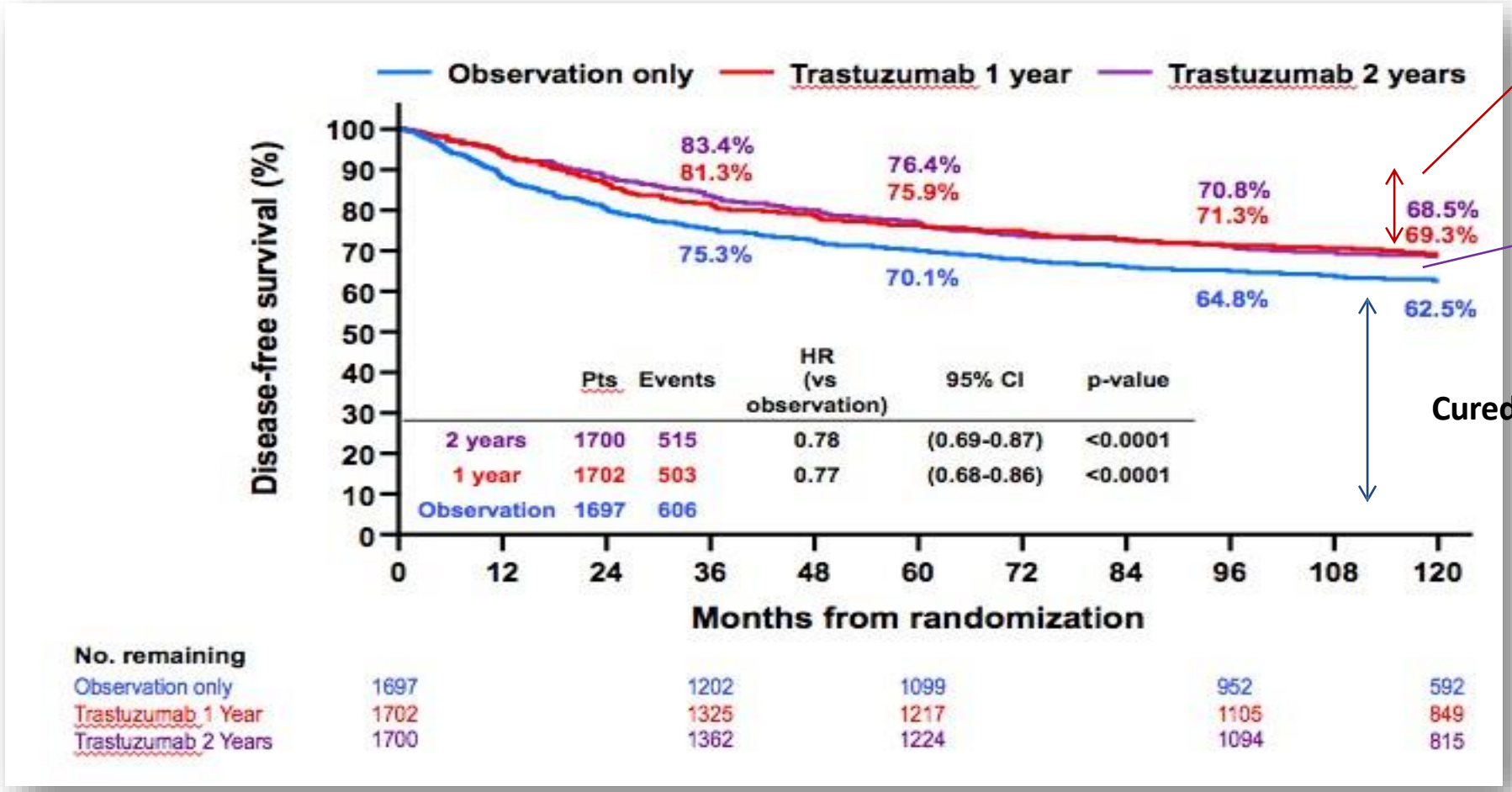
Adapted from Piccart-Gebhart MJ, ASCO 2018.

1. Pivot X, et al. Lancet Oncol 2013; 2. Mavroudis D, et al. Ann Oncol 2015; 3. Earl HM, et al. Lancet. 2019; 4. Conte PF, et al. Ann Oncol 2018; 5. Joensuu H, et al. JAMA Oncol 2018.

ESMO

HERA results at 11 years FU

Why do we need more treatments?



Need more treatment

Benefit from trastuzumab

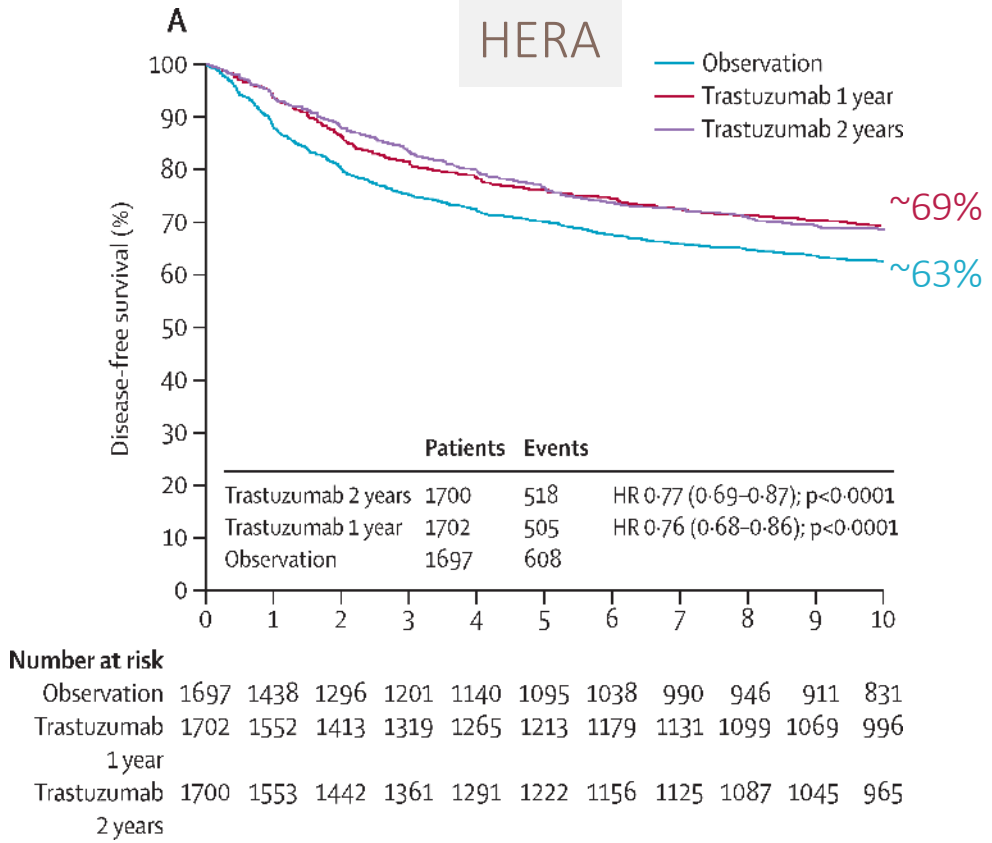
Cured by chemo

Cameron et al, Lancet 2017

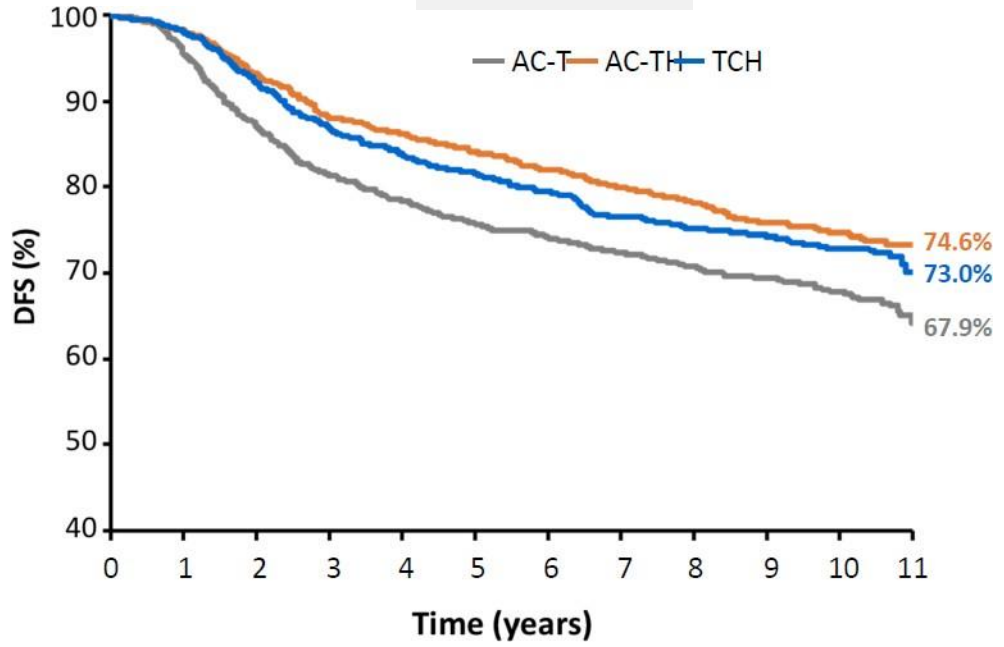
ADJUVANT TRASTUZUMAB + CHT

HERA and BCIRG 006 trials results (anthracycline +/- taxane OR anthracycline-free CHT)

HERA



BCIRG 006



Cameron D, et al. Lancet 2017
Slamon D, et al SABCS 2015

SMALL N- HER2+ EBC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Sara M. Tolaney, M.D., M.P.H., William T. Barry, Ph.D., Chau T. Dang, M.D., Denise A. Yardley, M.D., Beverly Moy, M.D., M.P.H., P. Kelly Marcom, M.D., Kathy S. Albain, M.D., Hope S. Rugo, M.D., Matthew Ellis, M.B., B.Chir., Ph.D., Iuliana Shapira, M.D., Antonio C. Wolff, M.D., Lisa A. Carey, M.D., Beth A. Overmoyer, M.D., Ann H. Partridge, M.D., M.P.H., Hao Guo, M.S., Clifford A. Hudis, M.D., Ian E. Krop, M.D., Ph.D., Harold J. Burstein, M.D., Ph.D., and Eric P. Winer, M.D.

Non randomized prospective trial

N = 406
T ≤ 3 cm N0
(T1N0 = **91.1%**)

De-escalation

Surgery

wP x 12

Trastuzumab

Primary endpoint
3 year-rate of invasive disease of ≤5%

SMALL N- HER2+ EBC

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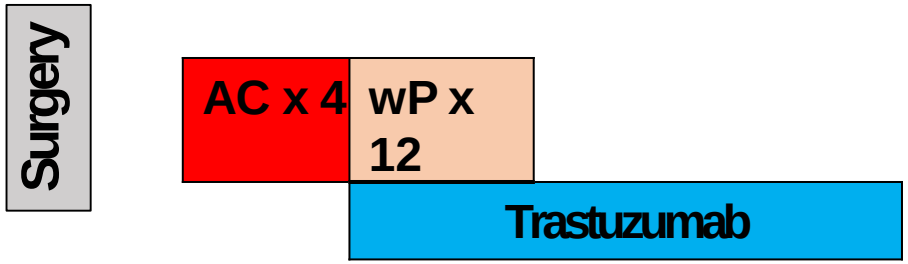


Primary endpoint
3 year-rate of invasive disease of ≤5%

ADJUVANT DE-ESCALATION STRATEGIES

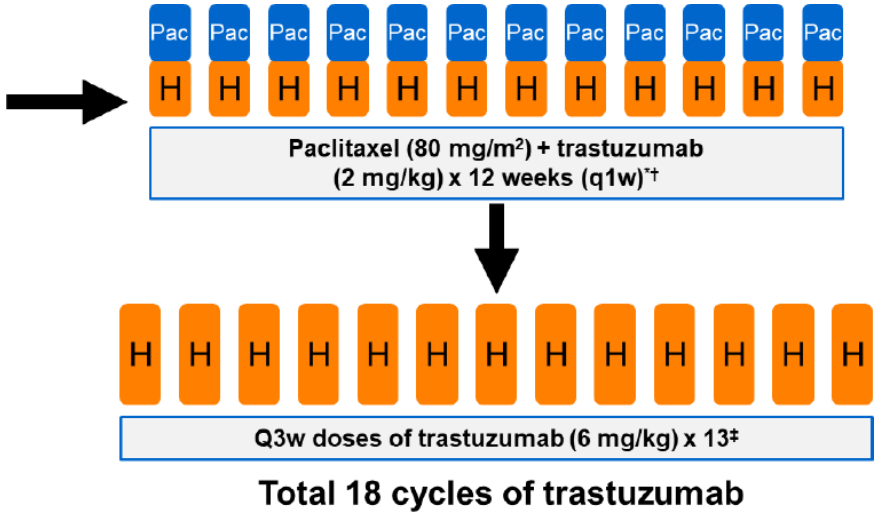
APT trial (**anthracycline-free** CHT)

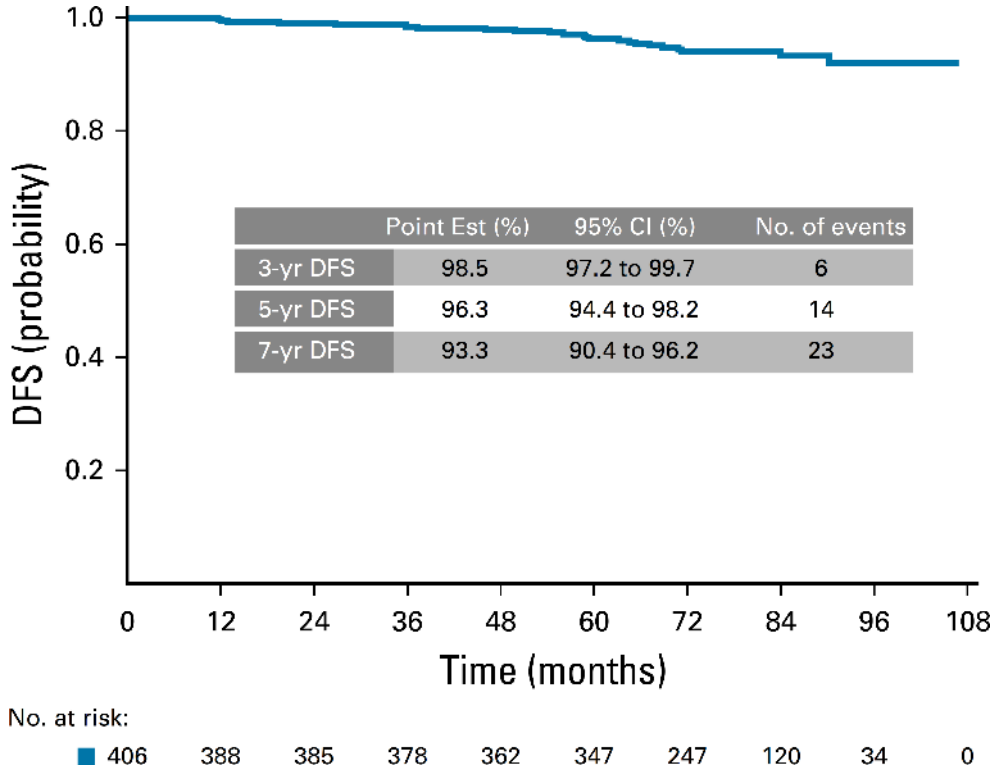
- **HER2-positive**
- **ER+ or ER–**
- **Node-negative tumour ≤3 cm**

N = 406

Primary endpoint:

Invasive DFS





	Point Est (%)	95% CI (%)	No. of events
3-yr DFS	98.5	97.2 to 99.7	6
5-yr DFS	96.3	94.4 to 98.2	14
7-yr DFS	93.3	90.4 to 96.2	23

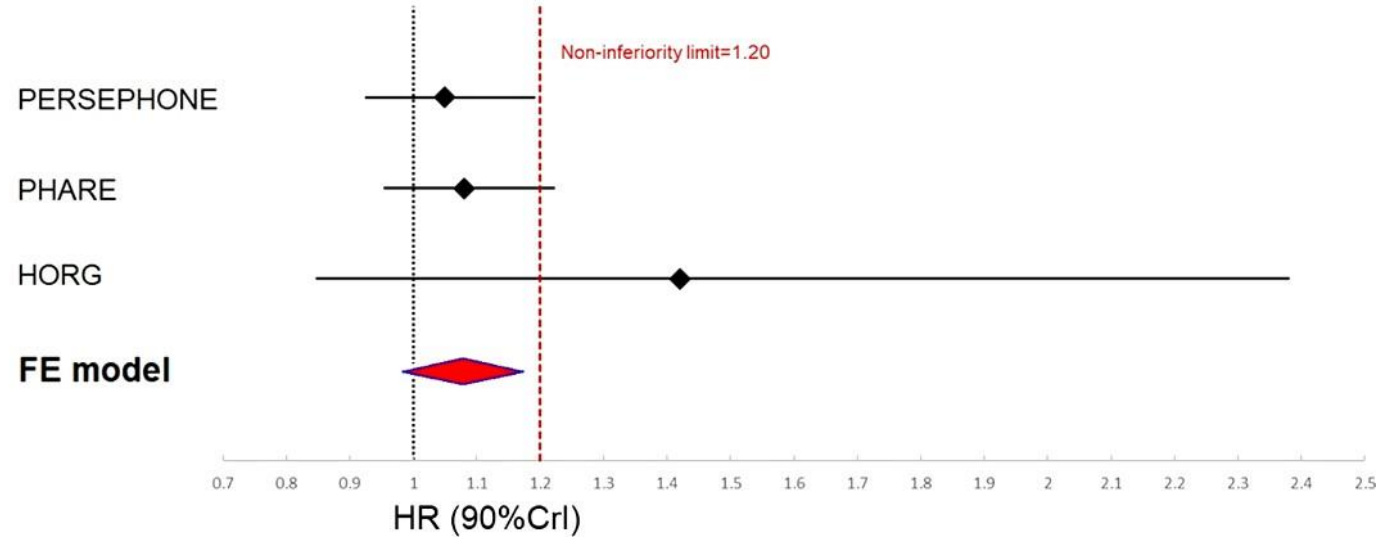
Tolaney SM, et al. JCO 2019

ADJUVANT DE-ESCALATION STRATEGIES

Meta-analysis of 5 non-inferiority RCTs: trastuzumab **12 months vs 6 months/9 weeks**

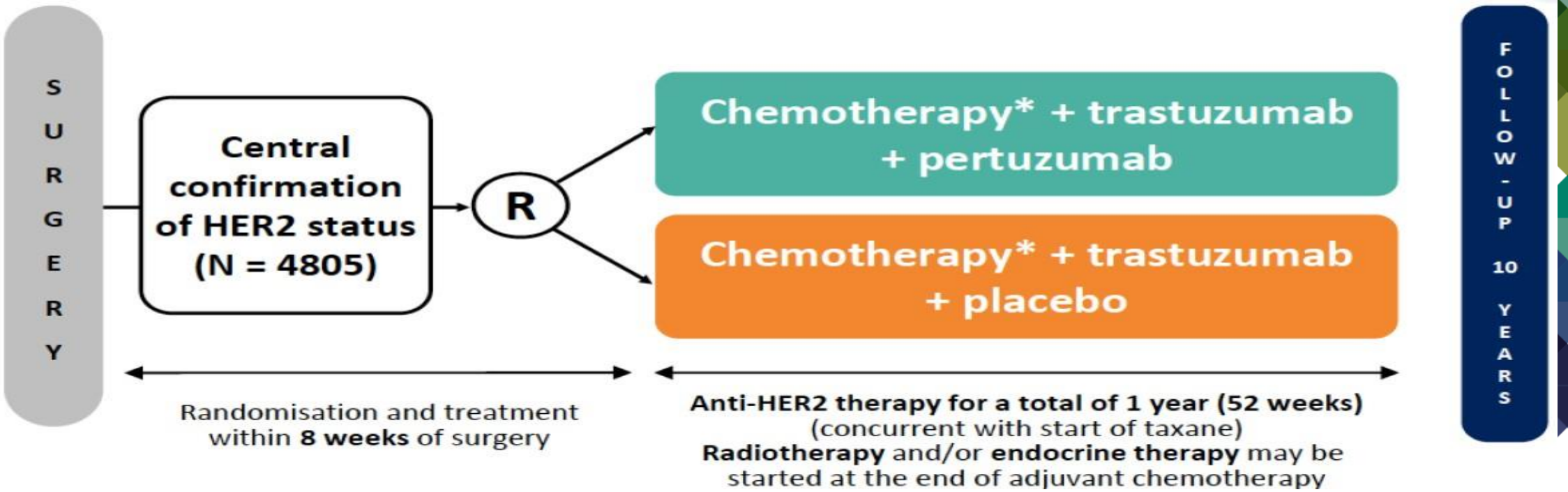
Results: 12m v 6m (3 trials combined – Fixed effects model)

For 12m v 6m, 5-year IDFS rates were 89.26% and 88.56% respectively.
The adjusted HR for treatment was 1.07 (90% CrI 0.98-1.17), non-inferiority p=0.02.



Earl HM, et al. ESMO 2021

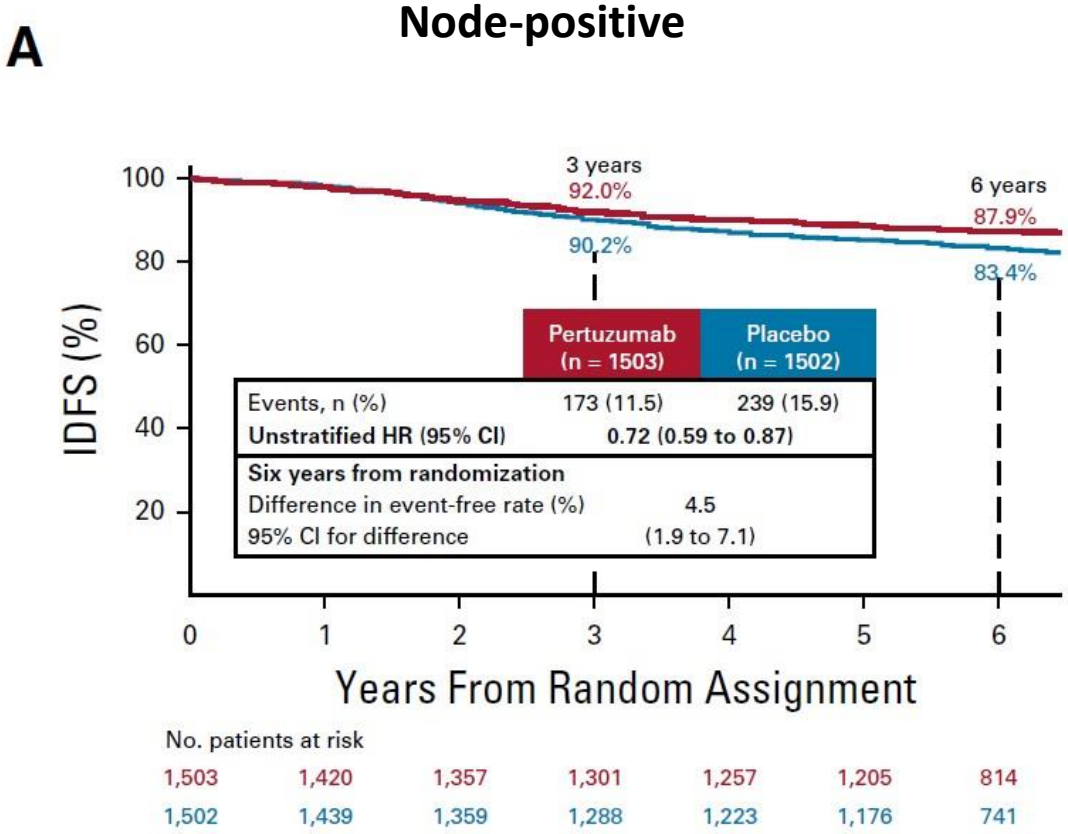
Addition of Pertuzumab: APHINITY



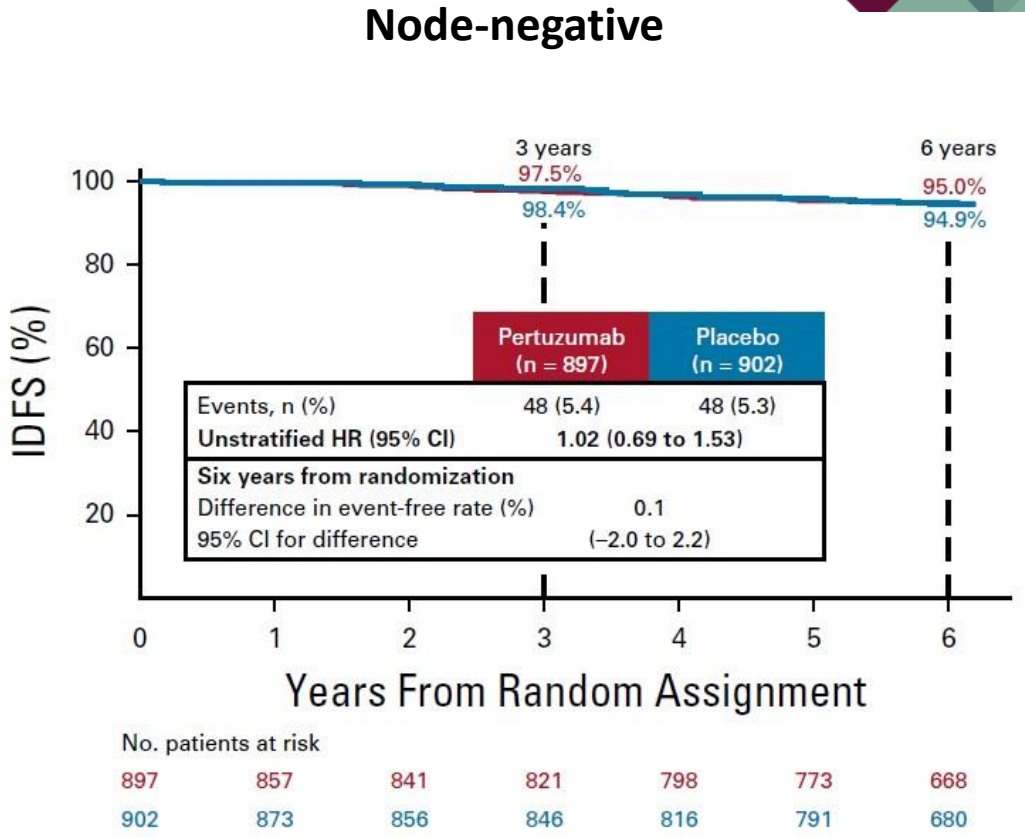
Von Minckwitz G et al, NEJM, 2018

APHINITY Updated descriptive analysis 74.1 months median FU
Time to first IDFS event by treatment regimen and nodal status

Node-positive



Node-negative

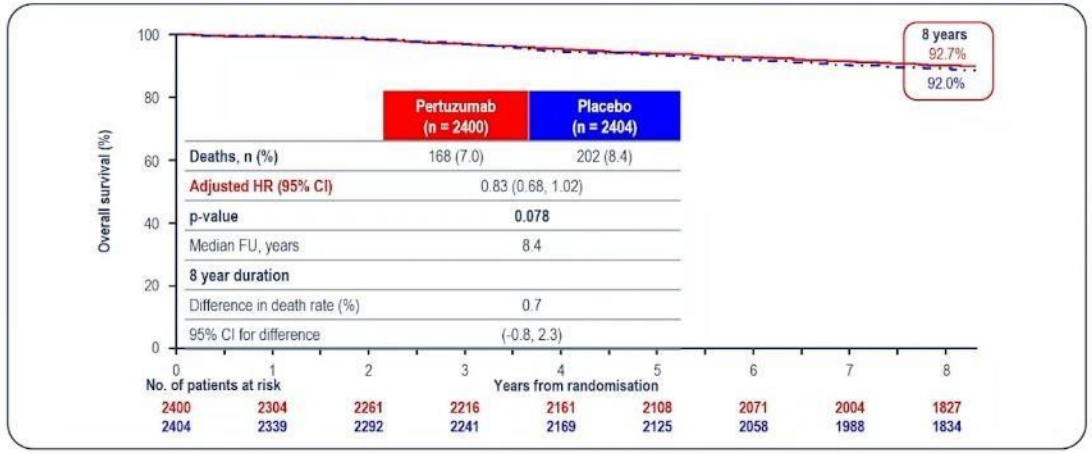


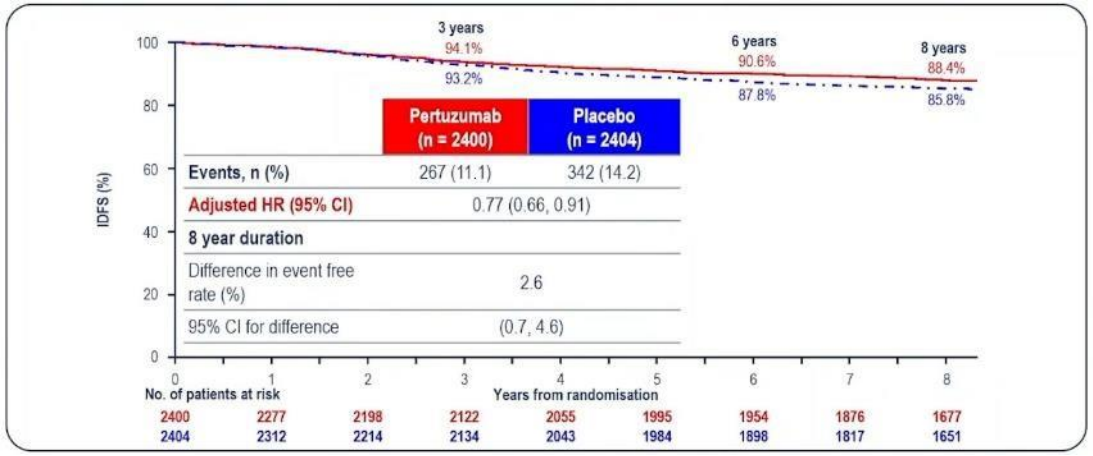
Piccart-Gebhart, J Clin Oncol 2020

ADJUVANT TRASTUZUMAB + PERTUZUMAB

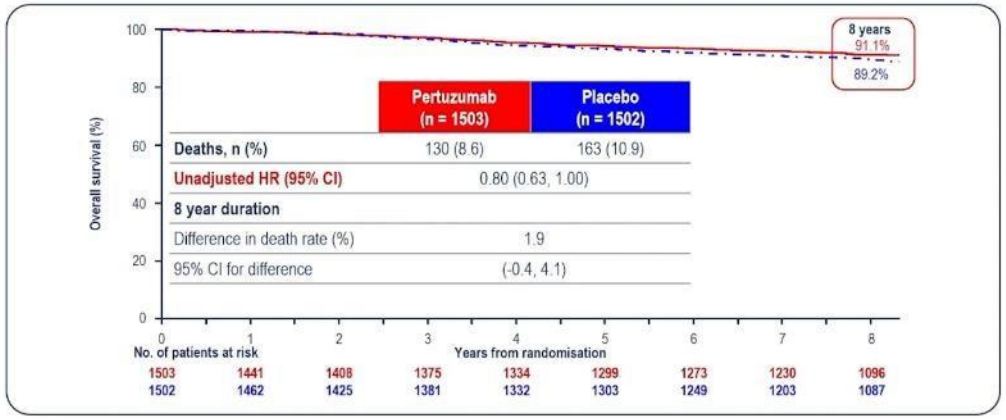
3rd interim OS analysis at 8.4 years median follow up (no benefit in node-negative population)

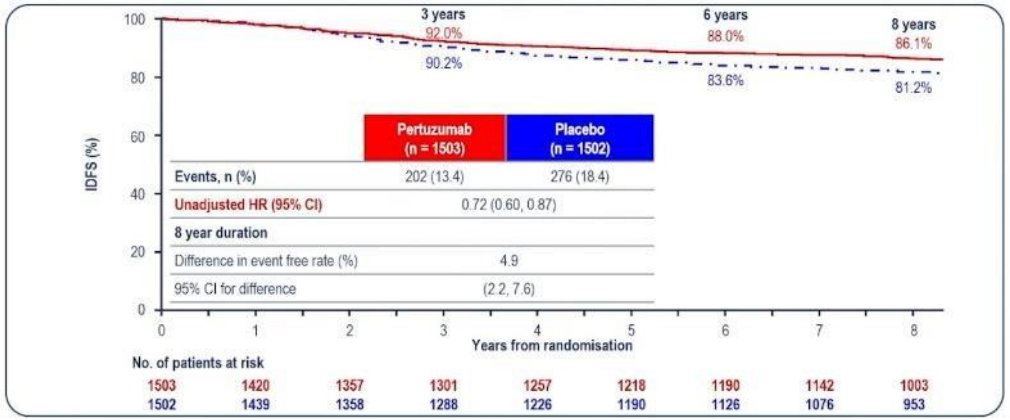
ITT population





Node-positive population

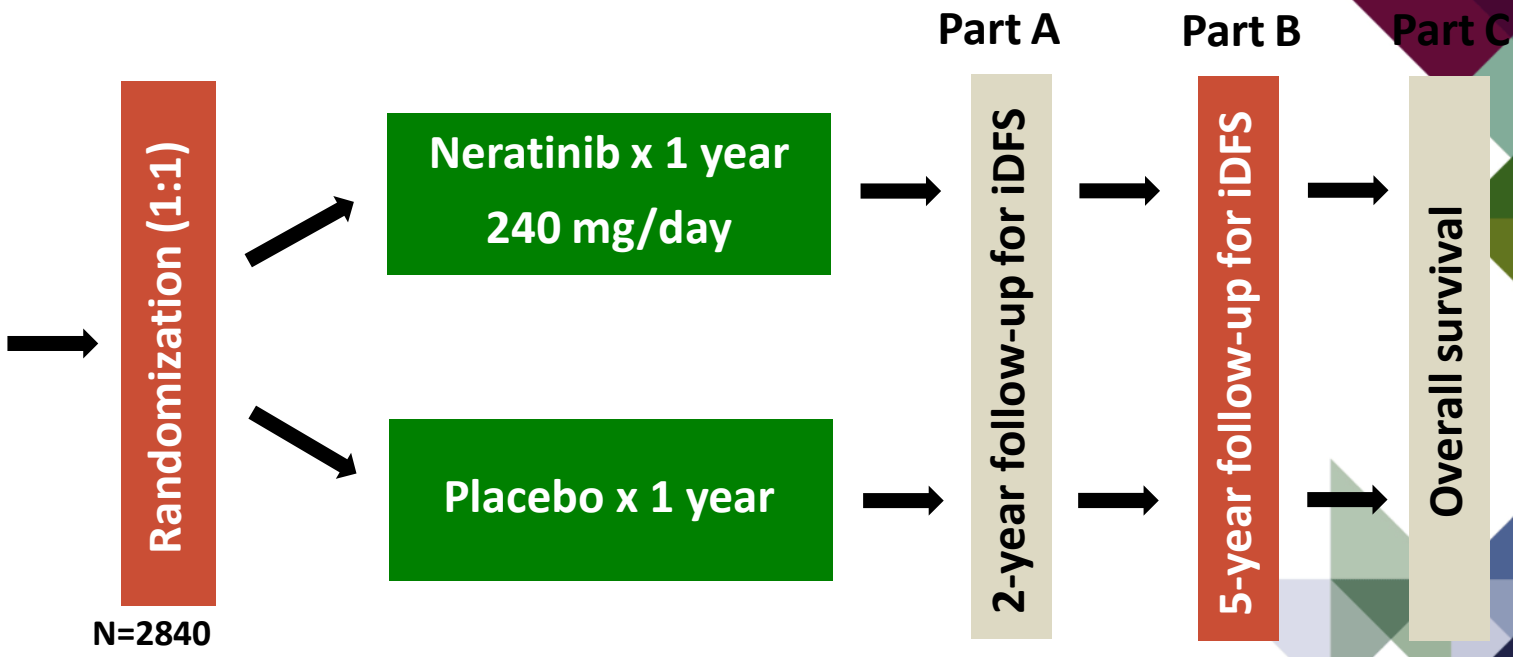




Loibl S, et al. ESMO Virtual Plenary July 2022

ExteNET: study design

- **HER2+ breast cancer**
  - IHC 3+ or ISH amplified (locally determined)
    - Prior adjuvant trastuzumab + chemotherapy
    - Lymph node +/–, or residual invasive disease after neoadjuvant therapy
- **Stratified by:** nodal status, hormone receptor status, concurrent *vs* sequential trastuzumab



Primary endpoint: invasive disease-free survival (iDFS)

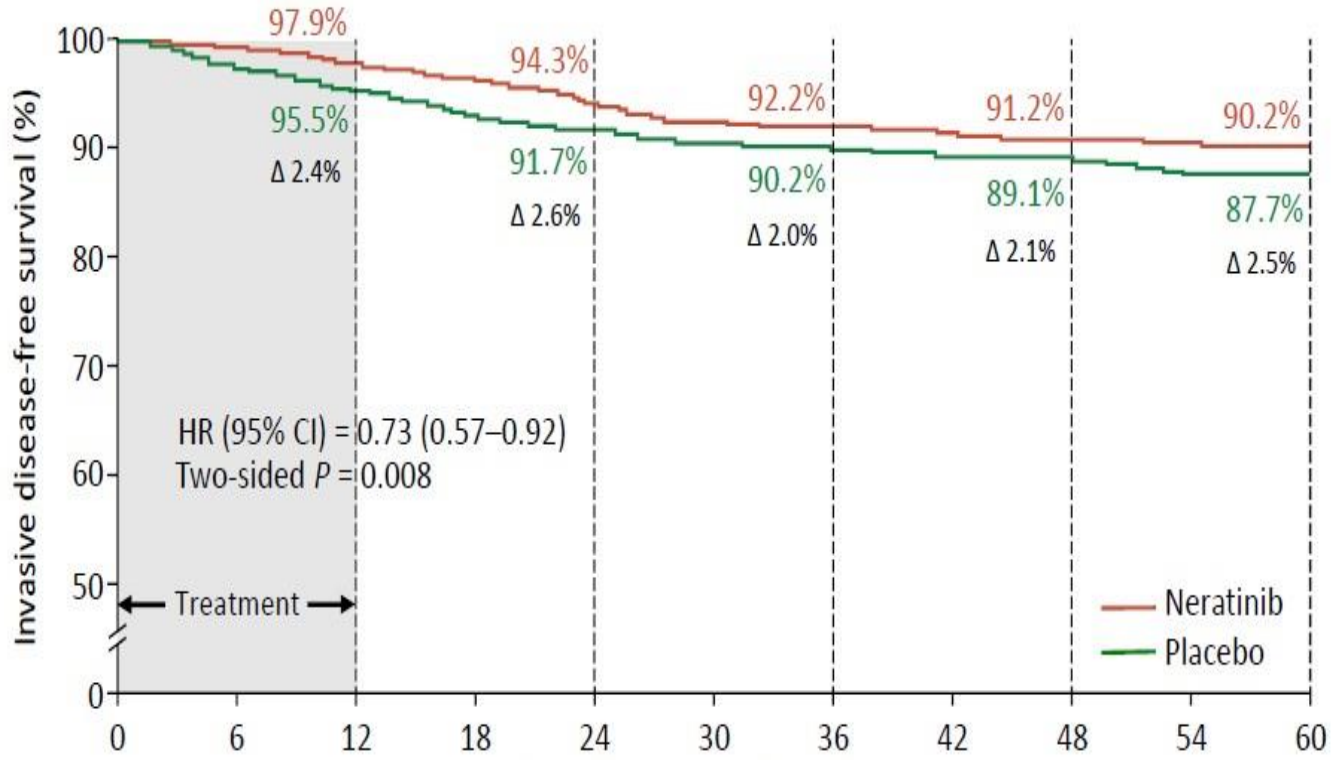
Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS recurrences, OS, safety

Other analyses: biomarkers, health outcome assessments (FACT-B, EQ-5D)

Endocrine adjuvant therapy given to patients with HR-positive tumors according to local practice

Chan et al. Lancet Oncol 2016

5-year analysis: iDFS

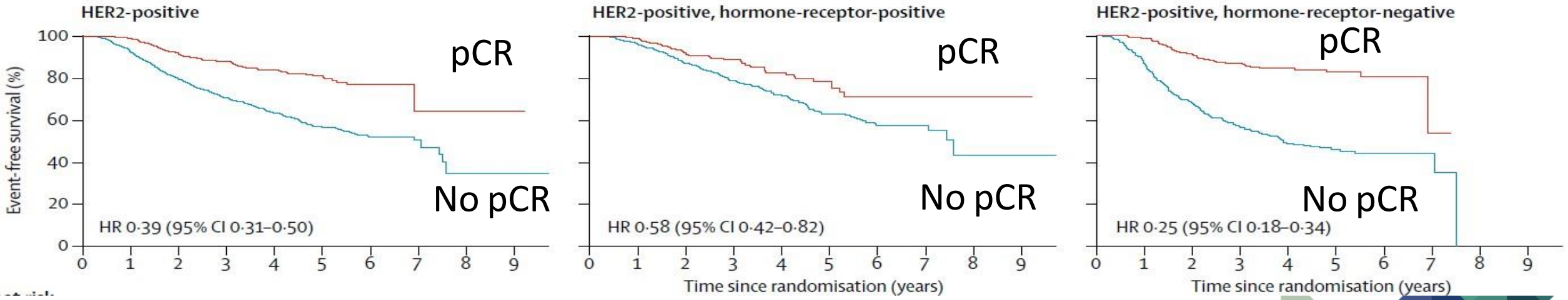


Benefit on HR-positive only

Intention-to-treat population. Cut-off date: March 1, 2017

Martins et al, ESMO 2017

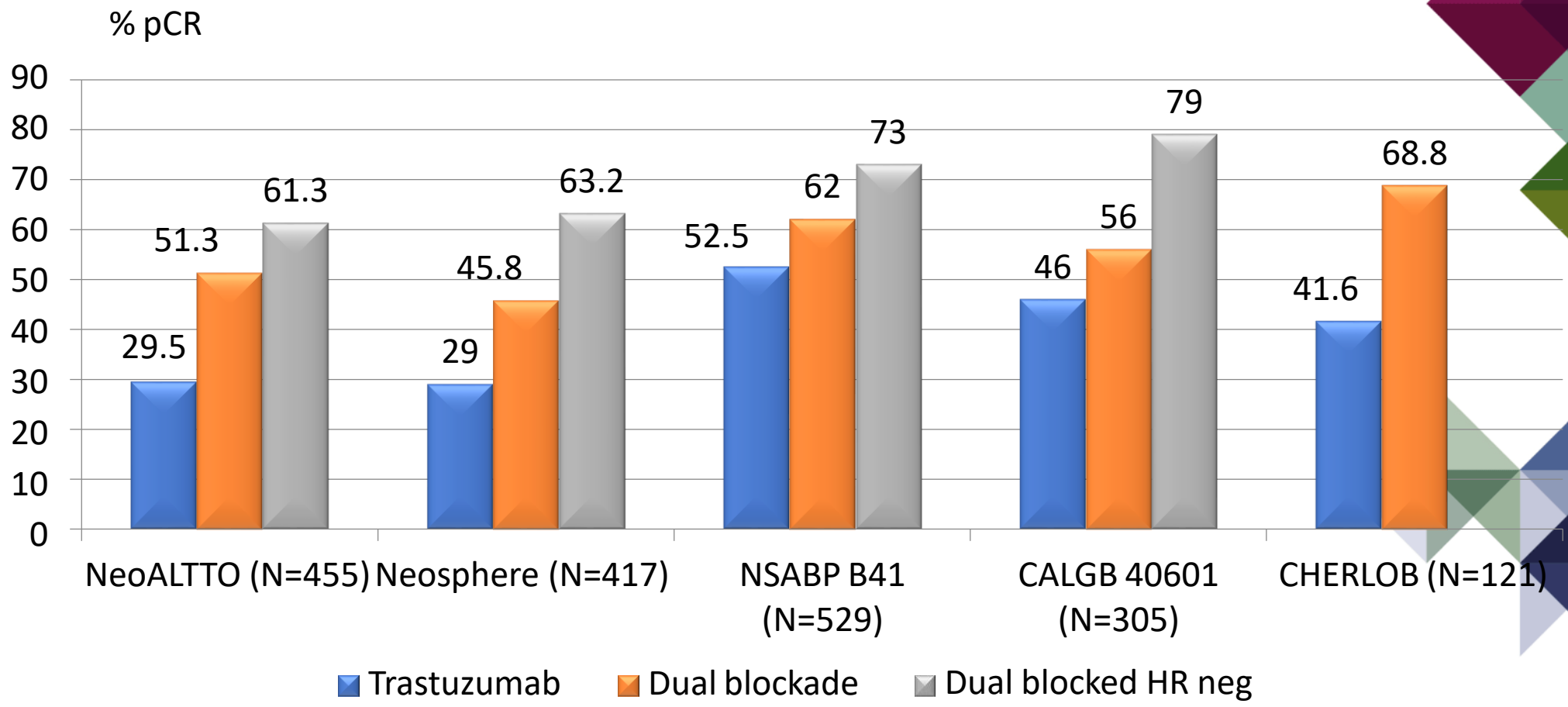
Correlation between pCR and outcomes



Incremental gain in pCR as a surrogate outcome
for EFS and OS
Surrogate at patient-level

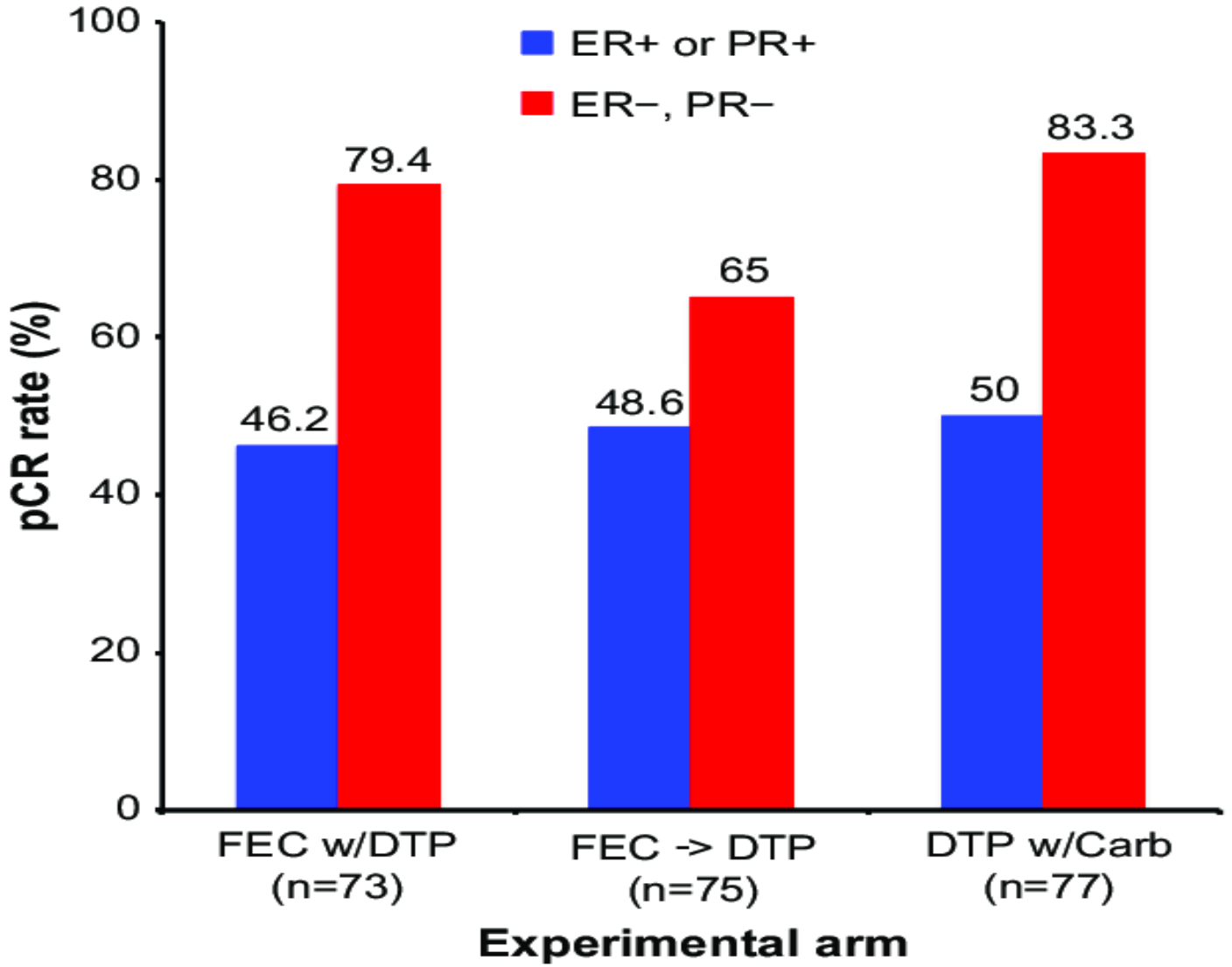
Cortazar P et al, Lancet Oncol, 2014

Dual blockade increases pCR rate



Baselga J et al, Lancet Oncol, 2012
Robidoux A et al, Lancet Oncol, 2013
Gianni L et al, Lancet Oncol, 2012
Guarneri V et al, J Clin Oncol 2012
Carey LA et al, J Clin Oncol 2016

Addition of Pertuzumab: TRYPHAENA



Gollamudi J et al, Cancer Management and Research, 2016

Post-neoadjuvant TDM1: KATHERINE

- Early HER2+ breast cancer patients
- Pertuzumab use was allowed
- Residual disease after neoadjuvant treatment with chemotherapy and trastuzumab

R
1:1

N=1.486

T-DM1
3.6mg/kg IV Q3W
14 cycles

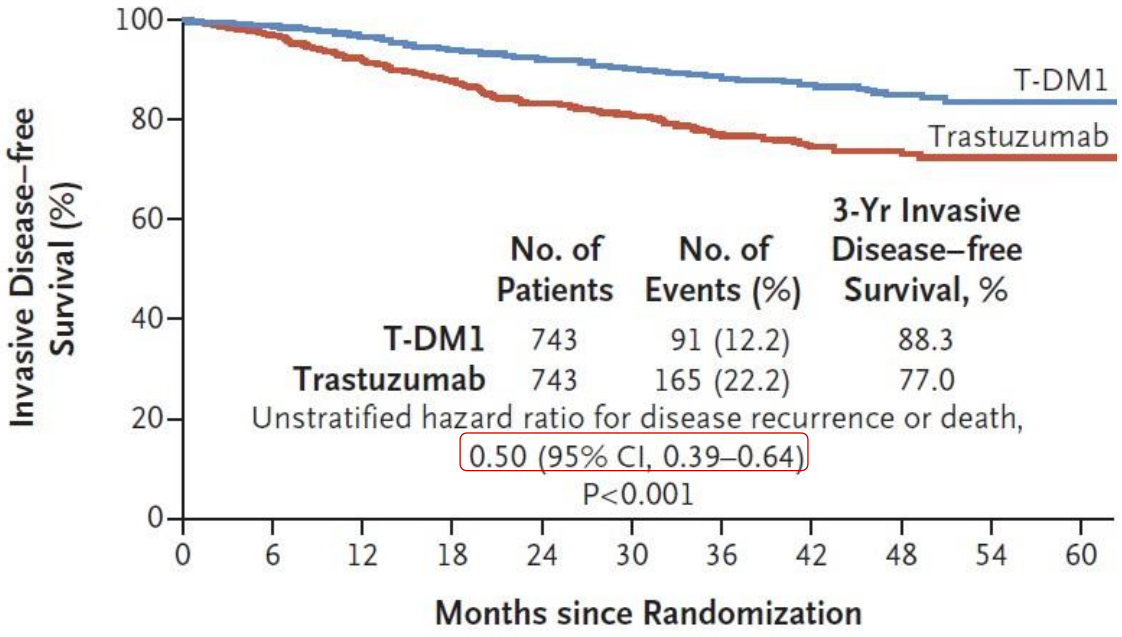
Trastuzumab
6 mg/kg IV Q3W
14 cycles

Radiation and endocrine treatment were administered according to local guidelines

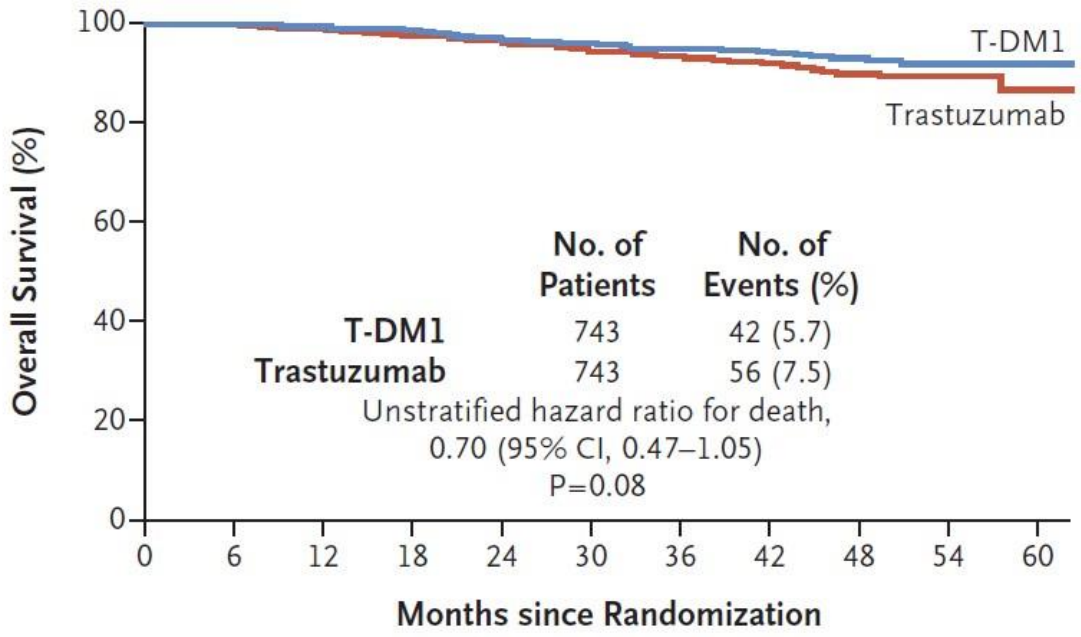
von Minckwitz et al, NEJM 2018

Post-neoadjuvant TDM1: KATHERINE

A



No. at Risk											
T-DM1	743	707	681	658	633	561	409	255	142	44	4
Trastuzumab	743	676	635	594	555	501	342	220	119	38	4



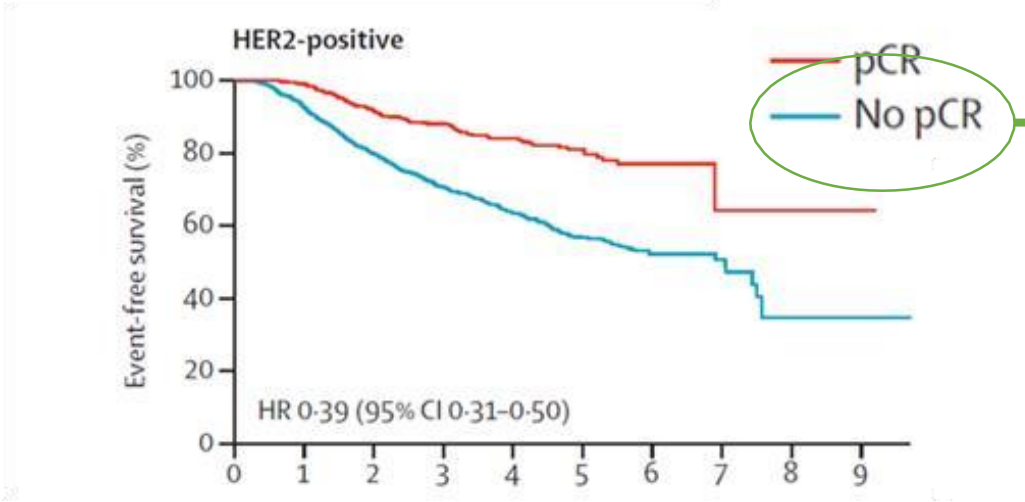
No. at Risk											
T-DM1	743	719	702	693	668	648	508	345	195	76	12
Trastuzumab	743	695	677	657	635	608	471	312	175	71	8

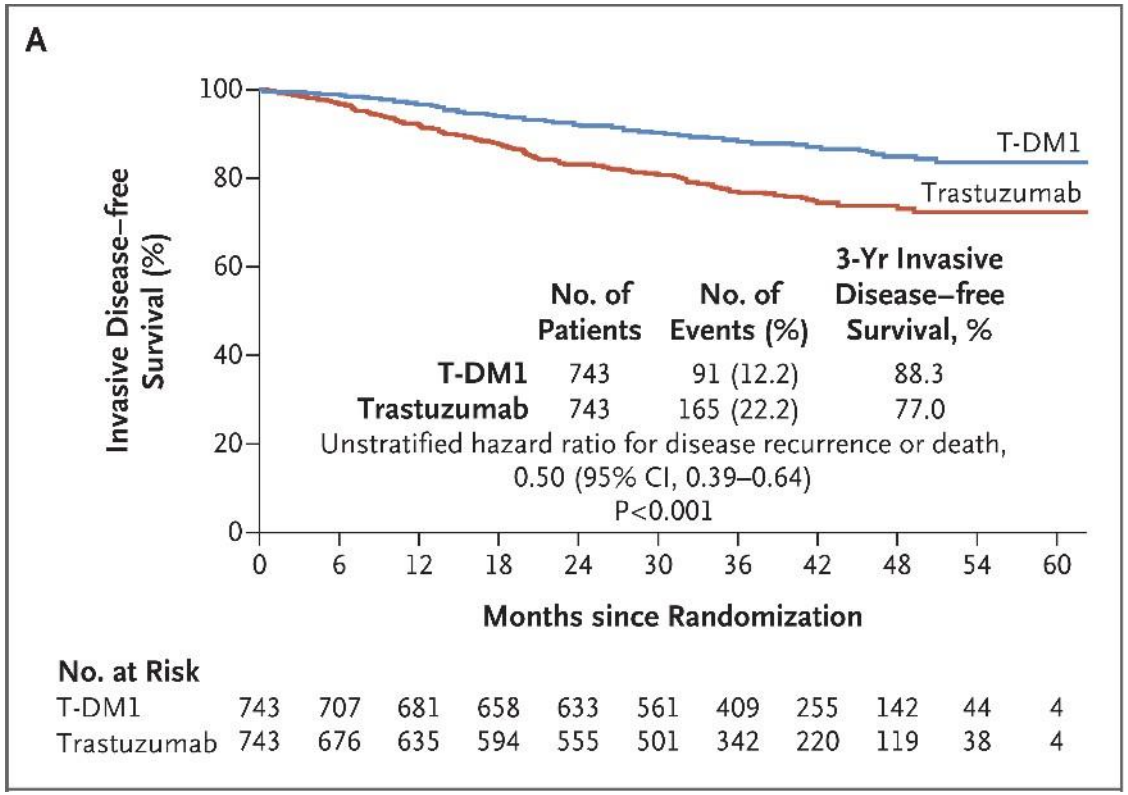
DDFS Δ 6.7%: HR 0.60 (95% CI 0.45-0.79)

von Minckwitz et al, NEJM 2018

POST-NEOADJUVANT ESCALATION STRATEGY

KATHERINE trial (**antibody-drug conjugate after residual disease**)



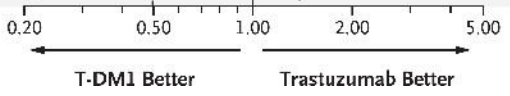


T-DM1 = trastuzumab emtansine

Cortazar P, et al. Lancet 2014
von Minckwitz G, et al. NEJM 2019

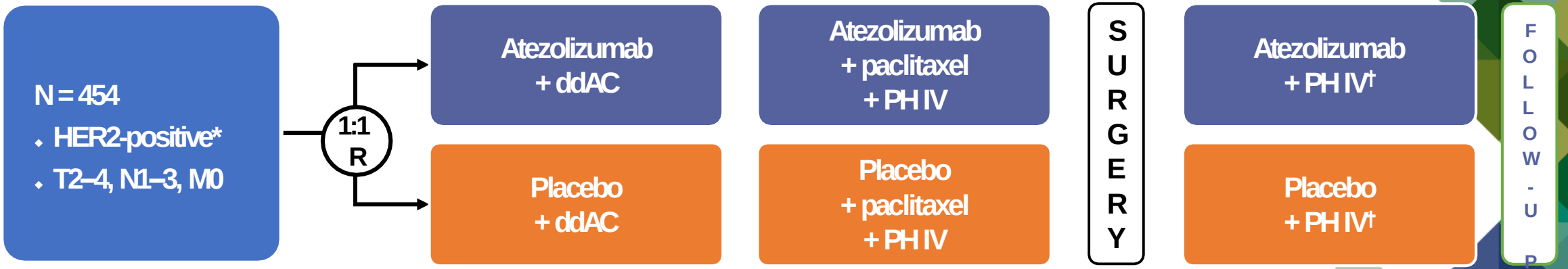
POST-NEOADJUVANT T-DM1 AFTER RESIDUAL DISEASE

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



von Minckwitz G, et al. NEJM 2019

IMpassion050: Study Design



Stratification factors:

- Stage T2 vs. T3-4
- ER-positive and/or PgR-positive vs. ER-negative and PgR-negative*
- PD-L1 IC 0 vs. IC 1/2/3*

Co-primary endpoints: pCR (ypT0/is ypN0) in the ITT and PD-L1-positive (IC 1/2/3; staining in ≥1% of tumour area) populations‡

Secondary endpoints: pCR in the PD-L1-negative (IC 0) population, EFS, OS, safety

Atezolizumab was given at 840 mg q2w during Cycles 1–4 and 1200 mg q3w thereafter; ddAC, at 60 mg/m²/600 mg/m² q2w; paclitaxel, at 80 mg/m² qw; P, at 840 mg during Cycle 5 and 420 mg q3w thereafter; H, at 8 mg/kg during Cycle 5 and 6 mg/kg q3w thereafter.

* Centrally assessed. Inclusion of patients with hormone receptor-positive disease was capped at 50%.

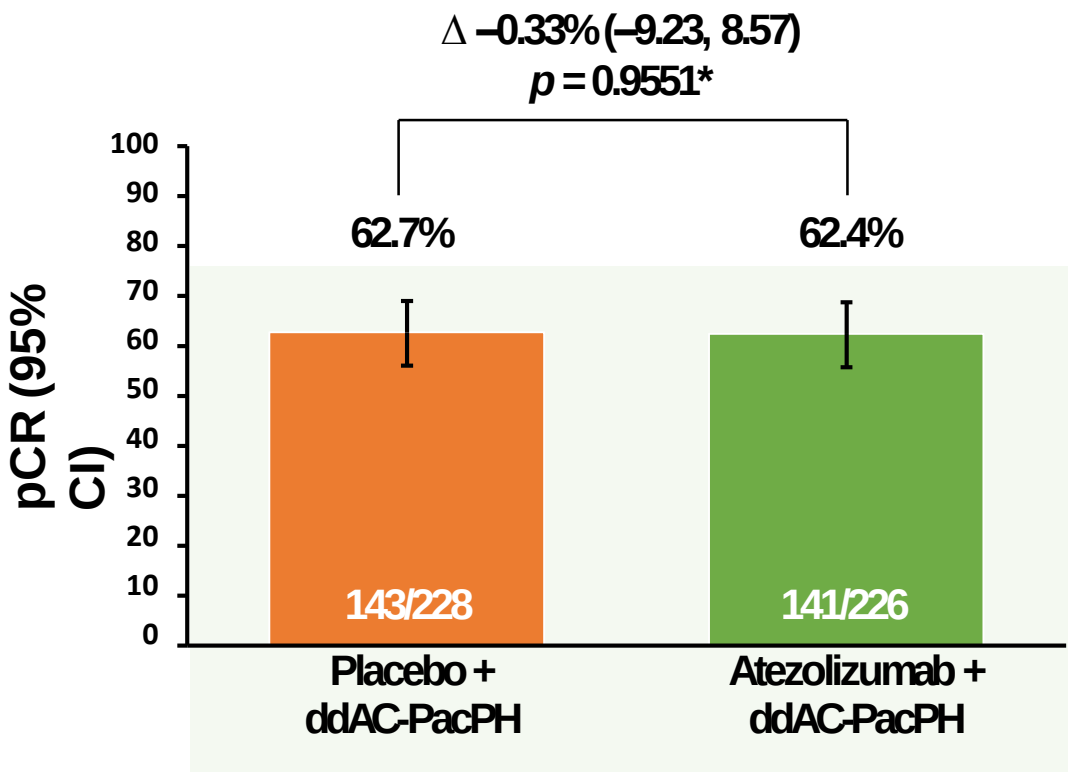
† Patients with residual disease could switch HER2-directed therapy to trastuzumab emtansine 3.6 mg/kg q3w at the discretion of the treating physician.

‡ Following a study amendment to co-power for PD-L1-positivity. PD-L1 staining was assessed using the VENTANA SP142 antibody.

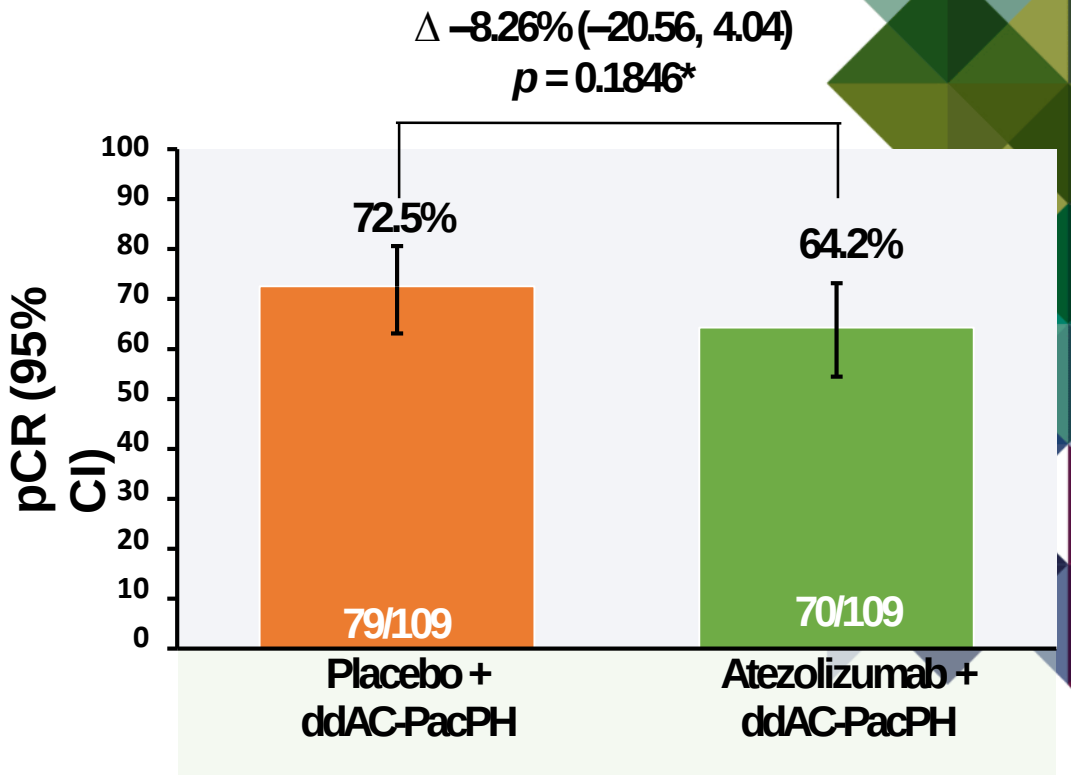
ddAC, dose-dense doxorubicin and cyclophosphamide; EFS, event-free survival; ER, oestrogen receptor; H, trastuzumab; ITT, intent-to-treat; IV, intravenous; OS, overall survival; P, pertuzumab; pCR, pathological complete response (ypT0/is ypN0); PD-L1 IC, PD-L1-expressing tumour-infiltrating immune cells as percentage of tumour area; PgR, progesterone receptor; q2w, every 2 weeks; q3w, every 3 weeks; qw, every week

Atezolizumab did not increase pCR rates vs. placebo in either the ITT or the PD-L1-positive population

ITT



PD-L1-positive



Assumptions

pCR 60% vs. 80% ITT and pCR 70% vs. 90%

https://bit.ly/3wSoe3d

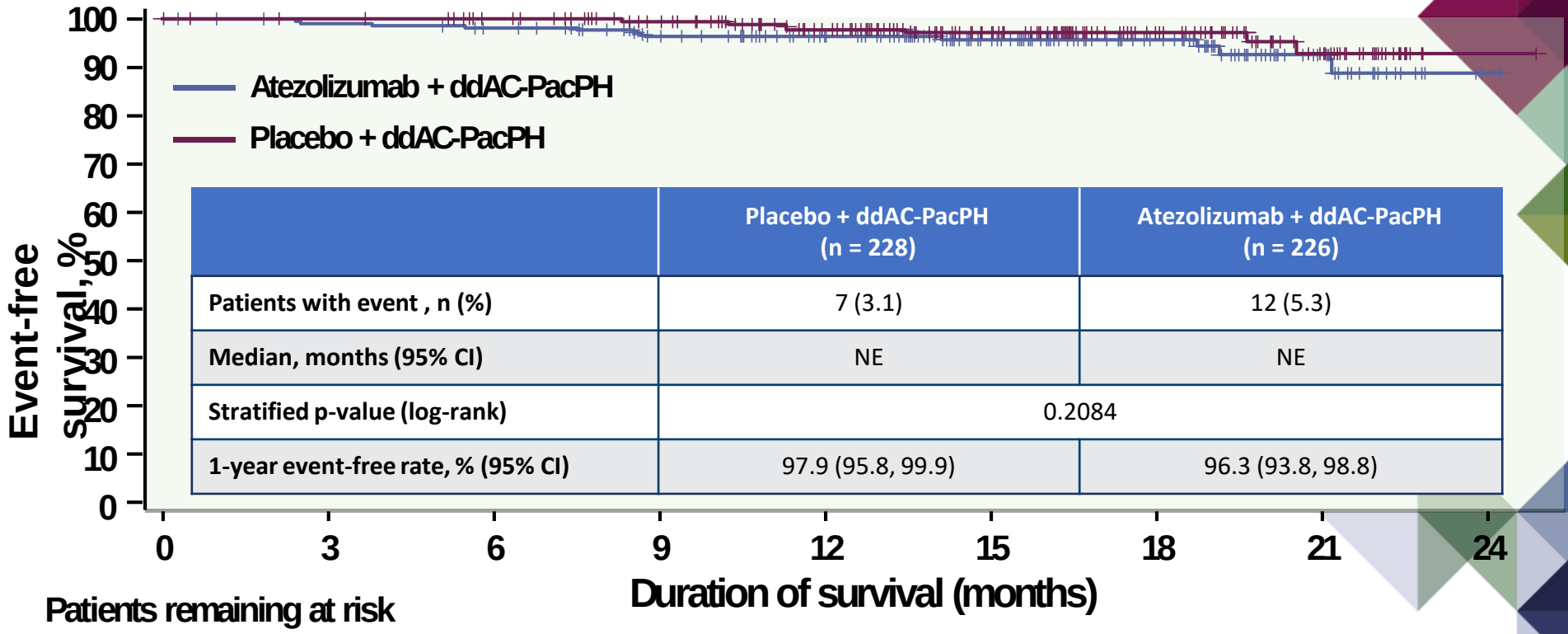
No benefit in any subgroup

*Stratified (Cochran-Mantel-Haenszel test).

CI, confidence interval; ddAC, dose-dense doxorubicin and cyclophosphamide; H, trastuzumab; ITT, intent-to-treat; P, pertuzumab; Pac, paclitaxel;
pCR, pathological complete response (ypT0/is ypN0).

ESMO

Event Free Survival (EFS) in the ITT population



	Placebo + ddAC-PacPH (n = 228)	Atezolizumab + ddAC-PacPH (n = 226)
Patients with event , n (%)	7 (3.1)	12 (5.3)
Median, months (95% CI)	NE	NE
Stratified p-value (log-rank)	0.2084	
1-year event-free rate, % (95% CI)	97.9 (95.8, 99.9)	96.3 (93.8, 98.8)

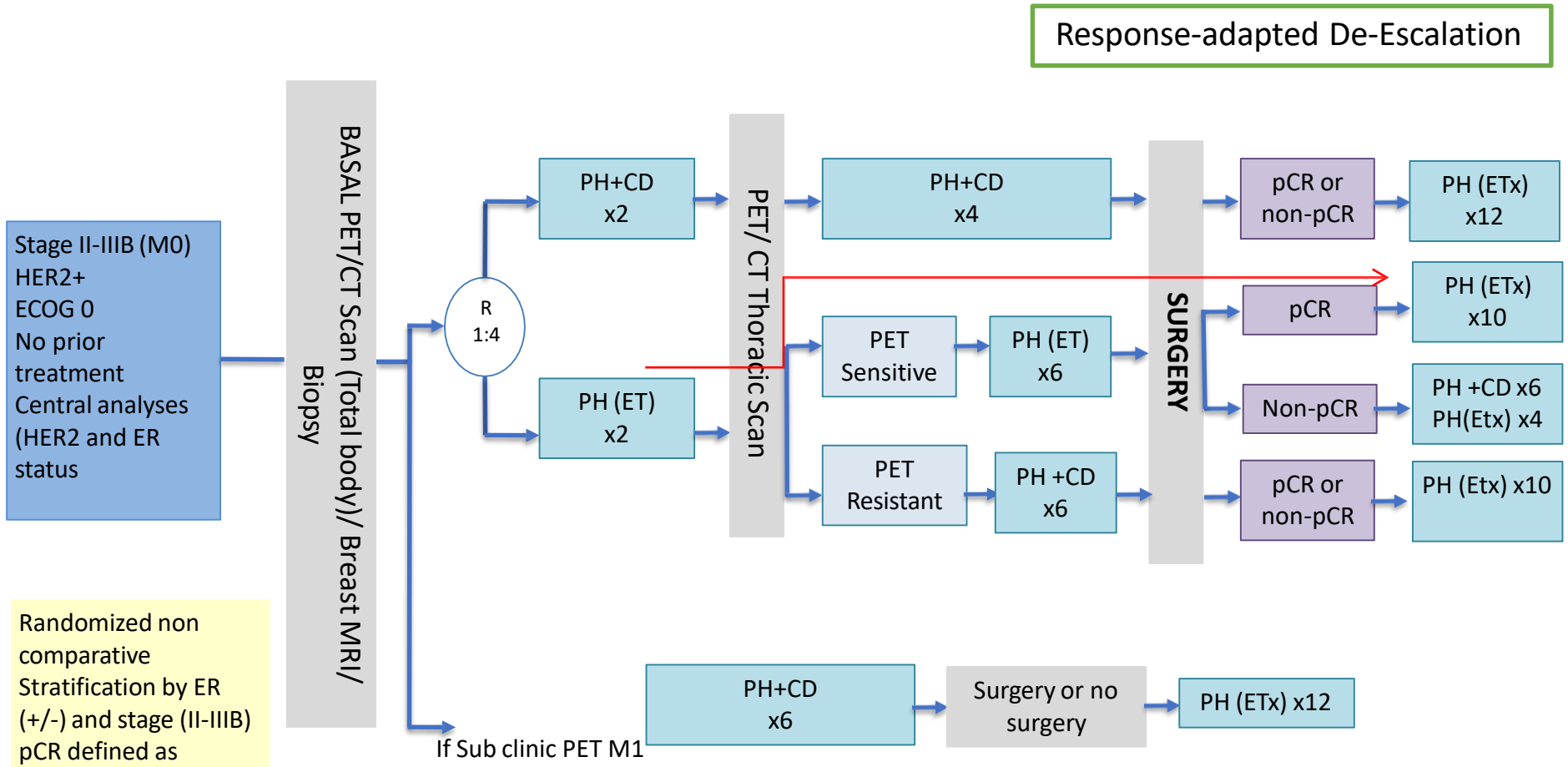
Patients remaining at risk

Atezolizumab + ddAC-PacPH	226	221	216	197	165	121	76	27	1
Placebo + ddAC-PacPH	228	224	217	201	169	123	69	32	1

Median follow-up: 15.7 mos in atezolizumab arm, and **15.9 mos** in placebo arm
→ **Data for EFS are immature**

CI, confidence interval; ddAC, dose-dense doxorubicin and cyclophosphamide; H, trastuzumab; ITT, intent-to-treat; NE, not evaluable; P, pertuzumab; Pac, paclitaxel.

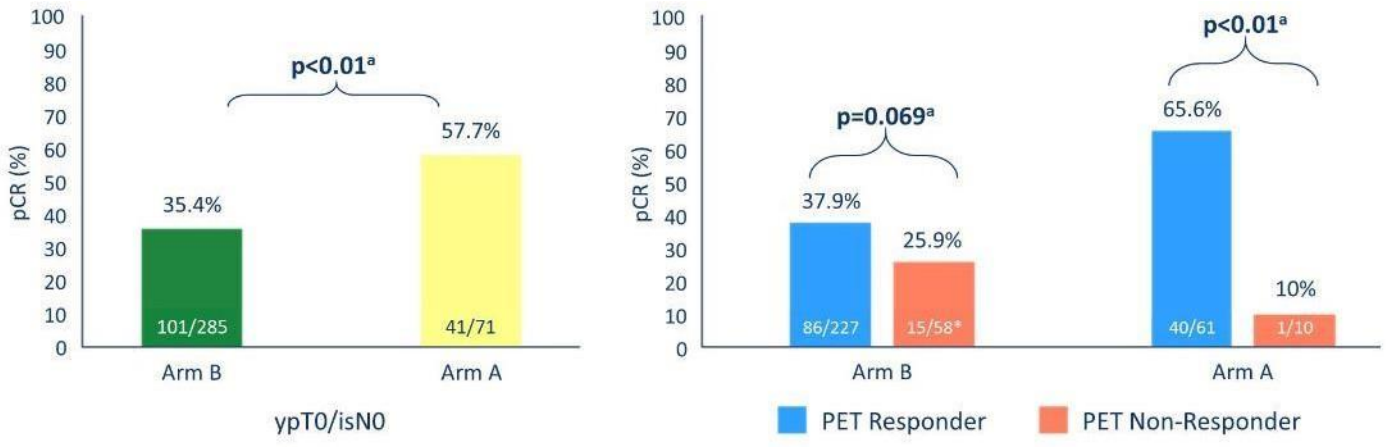
PHERGain trial



Randomized non comparative
Stratification by ER (+/-) and stage (II-IIIB)
pCR defined as ypT0/is,ypN0

H: Herceptin P: Perjeta C: carboplatin D: docetaxel Etx: endocrine therapy (letrozol or tamoxifen)
Adjuvant Etx for at least 5 years. All ER+ patients will receive Etx concomitantly with PH (except on chemo)

pCR in Arm B and Arm A



*These pts received TCHP.

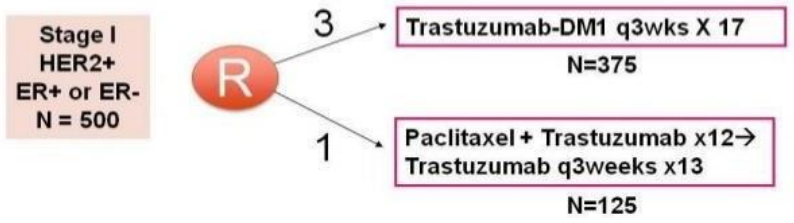
ªLogistic regression model adjusted by hormonal status, based on the Wald test.

PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response.

Waiting survival outcome data!!!

Presented By Javier Cortes at ASCO 2020

ATEMPT: Adjuvant HER2+ Trial (TBCRC 033)

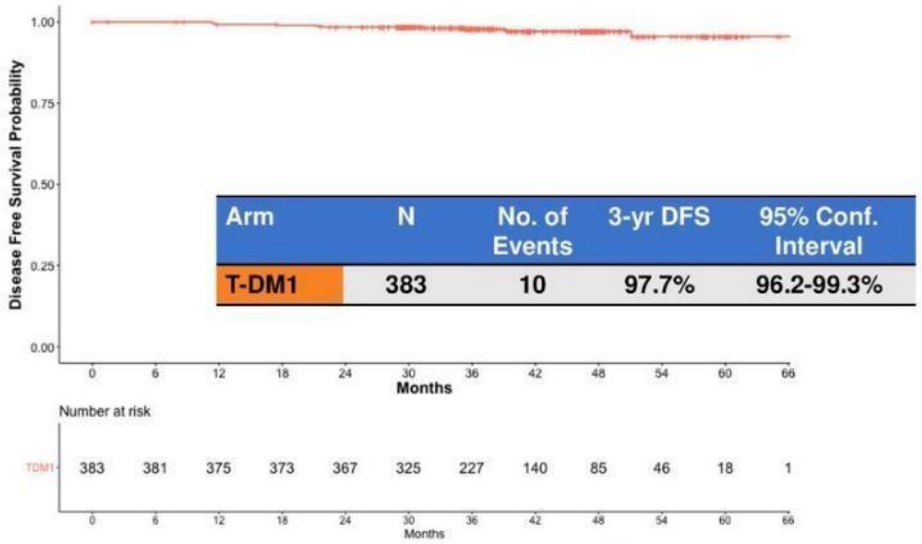


Primary endpoint to look for toxicity differences and a 3yr DFS of at least 95%

TH: more neurotoxicity (23% vs. 11%)
T-DM1: more discontinuation due to AE: 17% vs. 6%
TDM1: discontinued in 23.5%
Symptomatic **CHF**: 0.9% vs. 0.8%

Tolaney S, SABCS 2019

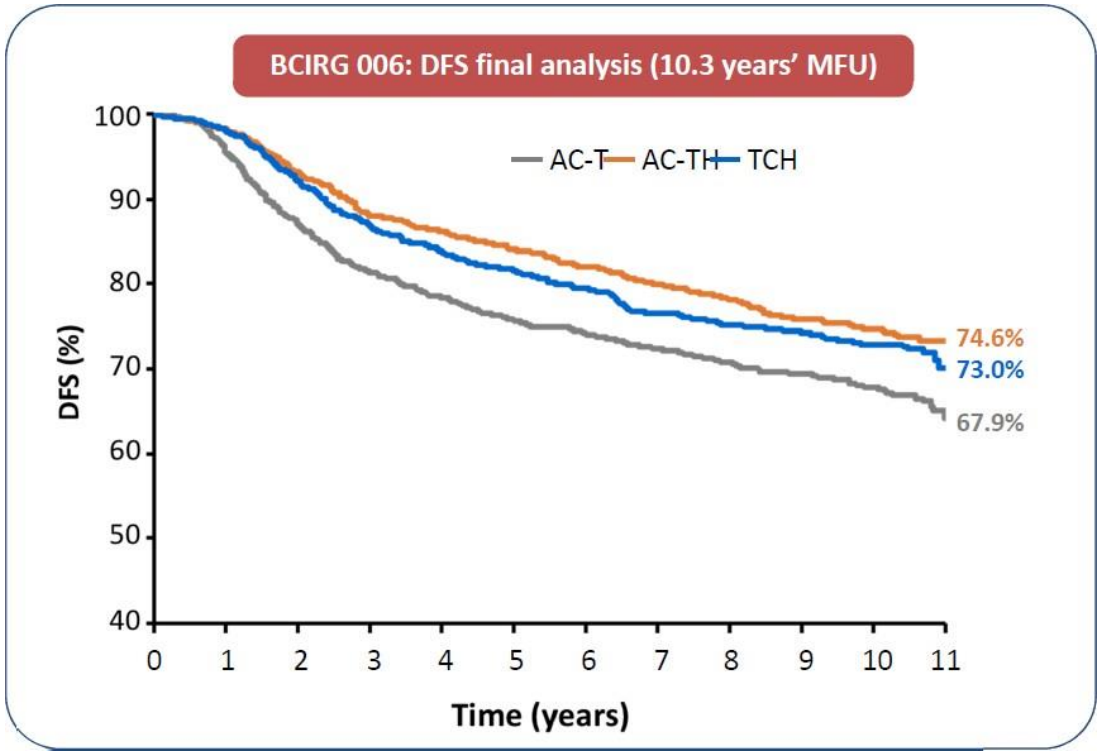
DISEASE-FREE SURVIVAL: T-DM1

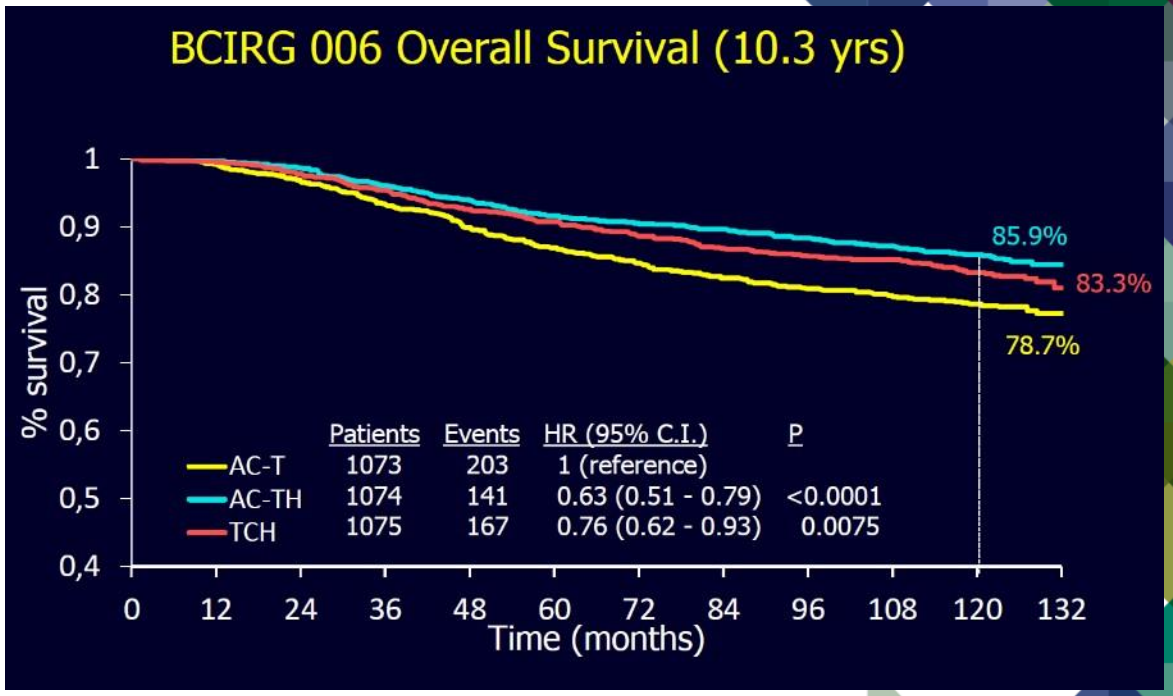


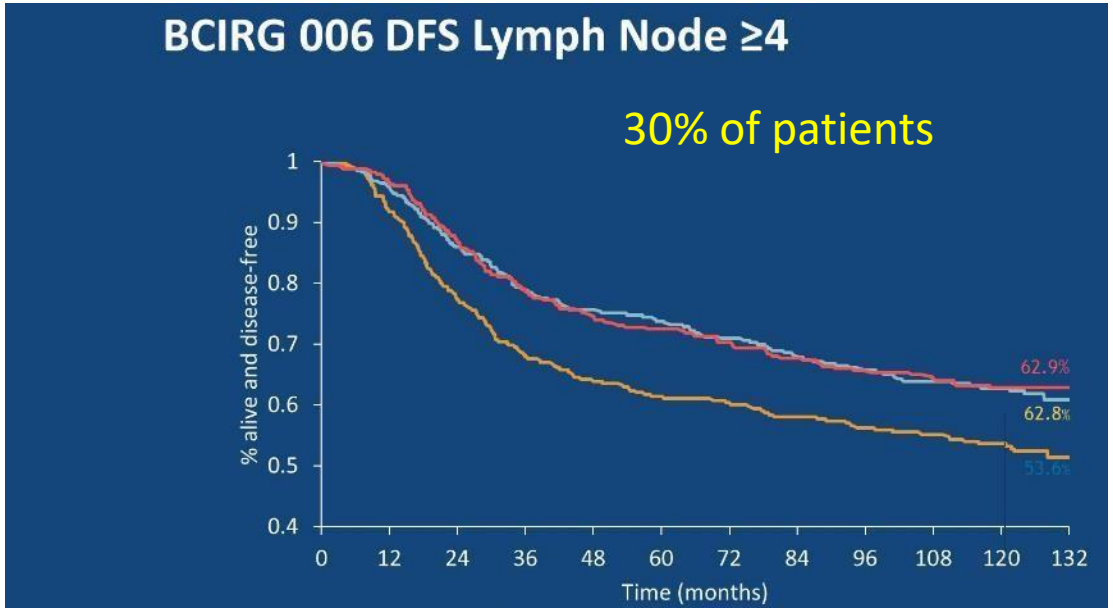
Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
T-DM1	383	10	97.7%	96.2-99.3%

p<0.0001

Do all patients need anthracyclines?







10-year report

- Similar DFS and OS
- TCH has less G3/4 arthralgia, myalgia, HFS, stomatitis, and vomiting
- Less Leukaemia

Slamon et al, SABCS 2015

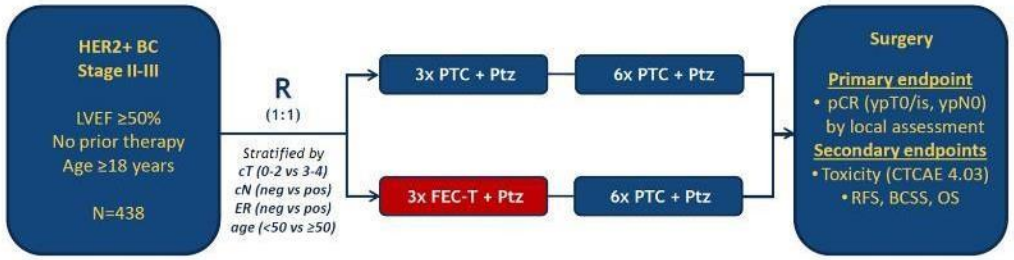
BCIRG 006: CARDIAC AES

AEs, n	AC → T (n = 1050)	AC → TH (n = 1068)	TCH (n = 1056)
Cardiac-related death	0	0	0
Grade 3/4 left ventricular function decline	8	21	4*
> 10% relative left ventricular ejection fraction decline	120	200	97†

*P = .0005 vs AC → TH.
†P < .0001 vs AC → TH.

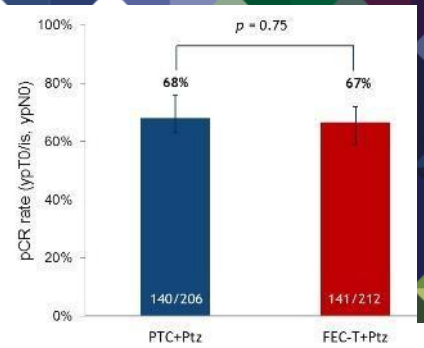
Slamon et al, SABCS 2015

TRAIN-2: study design

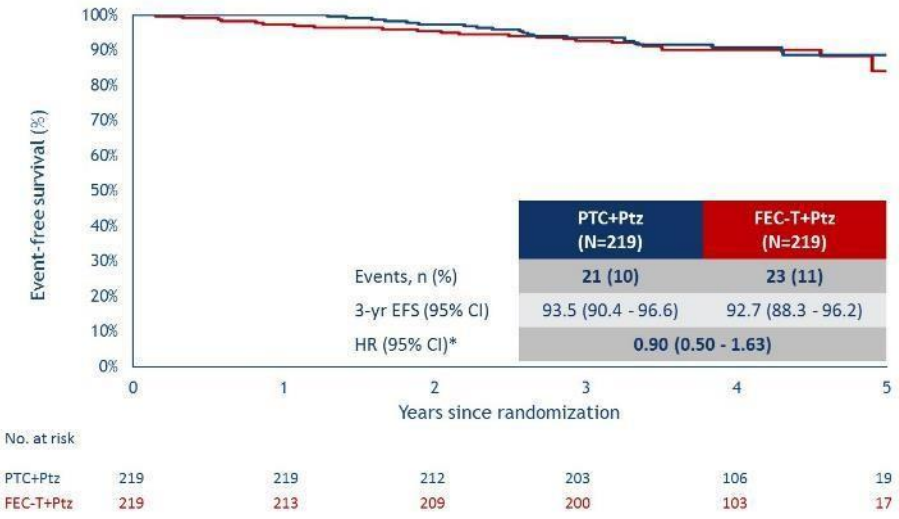


- PTC+Ptz cycle of 3 weeks, day 1 PTC+Ptz, day 8 only P: P = paclitaxel 80mg/m²; T = trastuzumab 6mg/kg (loading dose 8mg/kg); C = carboplatin AUC = 6mg·min/ml; Ptz = pertuzumab, 420mg (loading dose 840mg)
- FEC-T+Ptz cycle of 3 weeks: F = 5-fluorouracil 500mg/m²; E = epirubicin 90mg/m²; C = cyclophosphamide 500mg/m²;T = trastuzumab 6mg/kg (loading dose 8mg/kg); Ptz = pertuzumab, 420mg (loading dose 840mg)
- Adjuvant trastuzumab to complete one year of treatment and endocrine therapy for ER+ and/or PR+ tumors

van Ramshorst et al, *Lancet Oncol* 2018; van Ramshorst et al, *Eur J Cancer* 2017 — Clinicaltrials.gov identifier: NCT01996267



Event-Free Survival



*HR <1 favors PTC+Ptz

Anthracycline-based chemotherapy:

- More febrile neutropenia (10% vs. 1%)
- More cardiac toxicity: LVEF decrease ≥10% and LVEF <50% (8% vs. 3%, p 0.044)
- More secondary malignancies including leukaemia
- slight less neuropathy (5% vs. 7%)

van der Voort et al, ASCO 2020

ESMO

The future

DESTINY 11: Phase 3, open-label 3-arm Neoadjuvant Study

Population

HER2+ EBC

HR+ or HR-

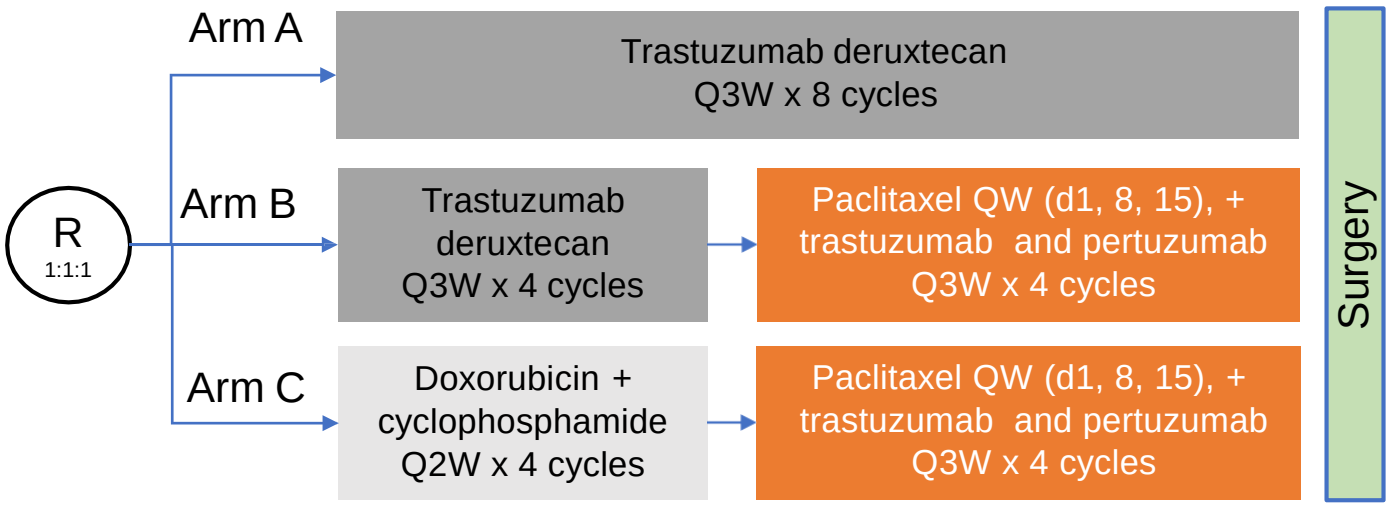
High-risk defined as one of the following:

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

Stratification factors:

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

Study Design



Post-neoadjuvant therapy will be determined by investigator and administered as per local SOC

Endpoints

Primary Endpoint:

- pCR (ypT0/Tis ypN0)

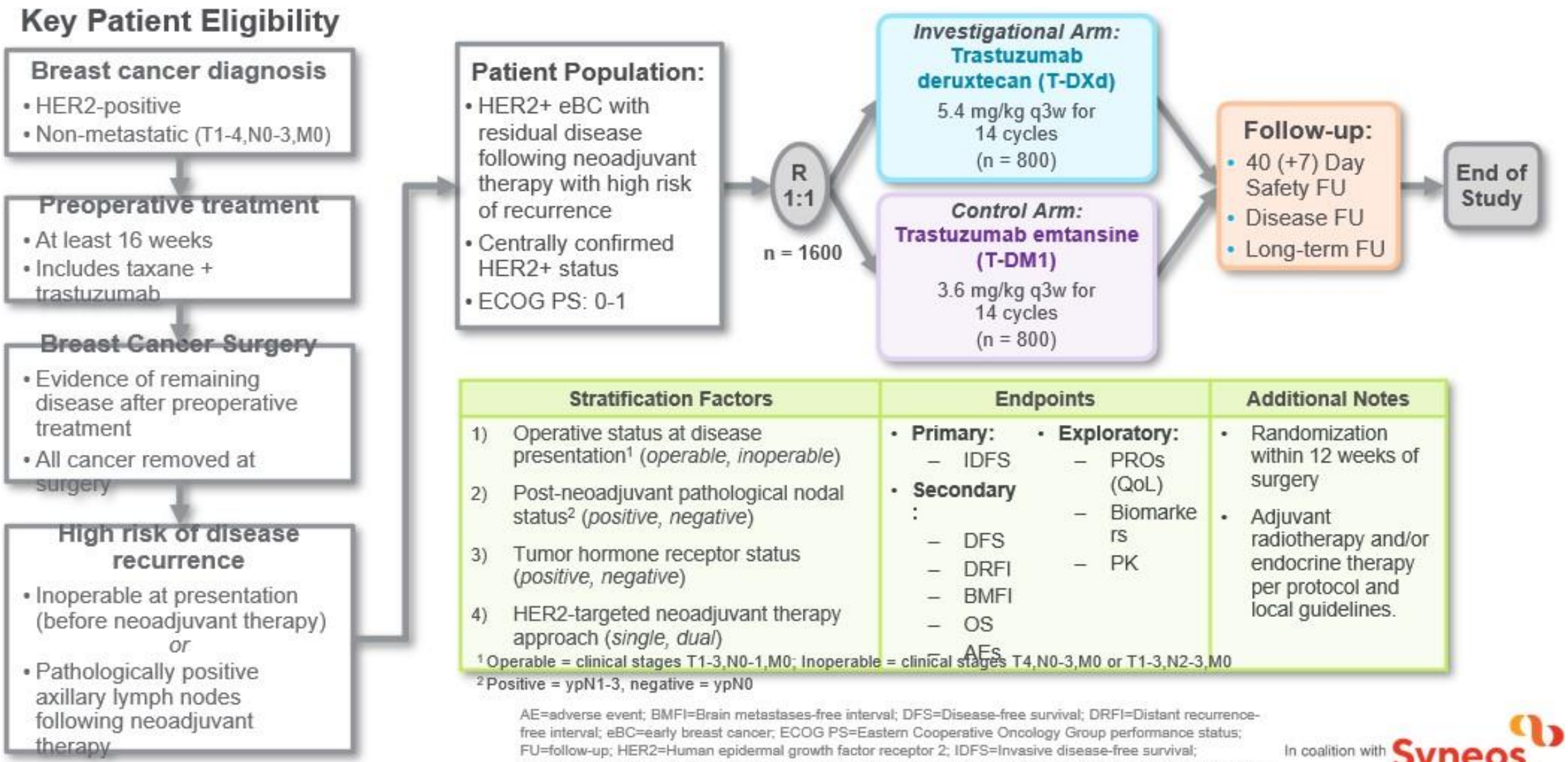
Secondary Endpoints:

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

Key Design Features:

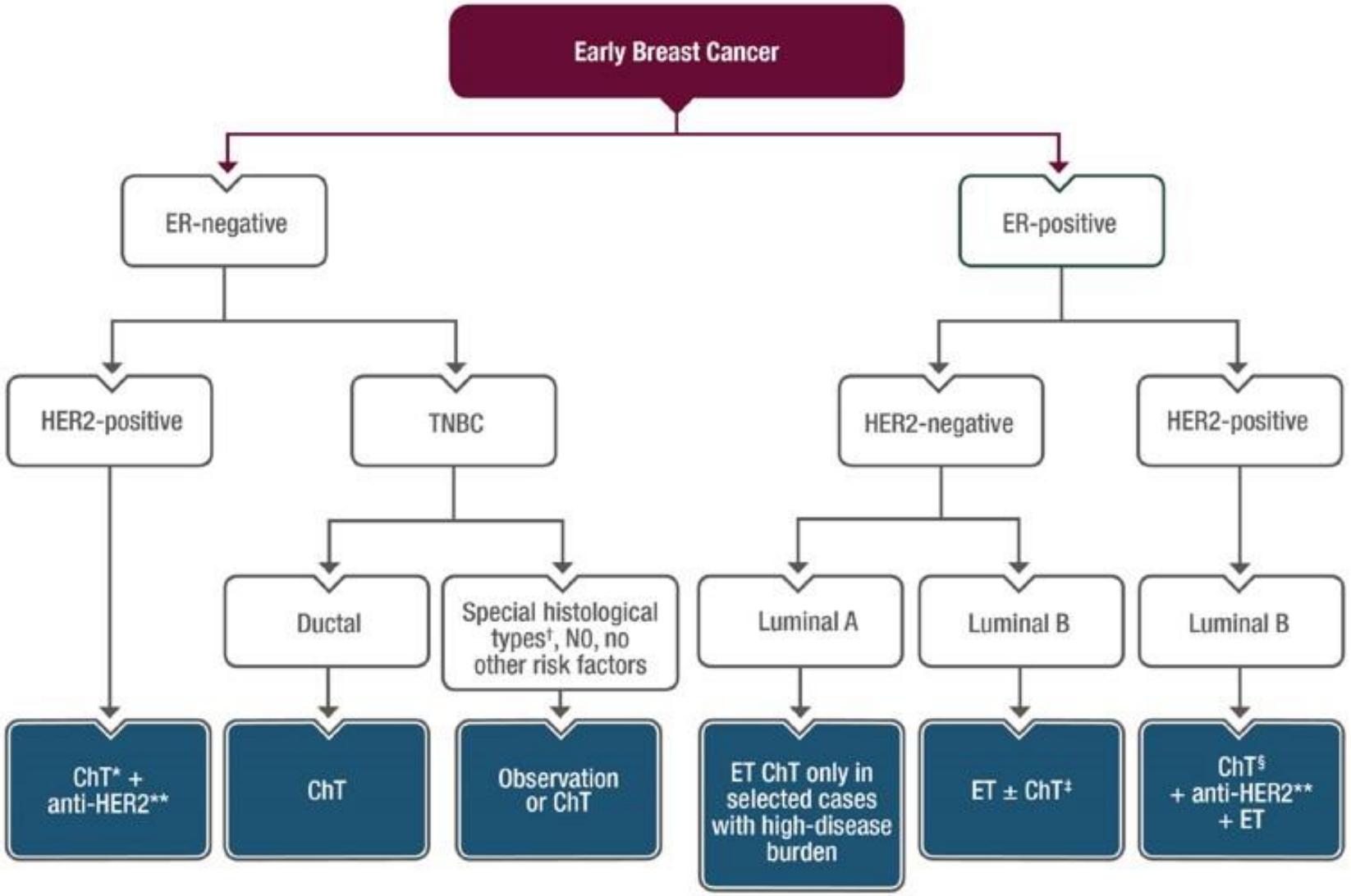
- Study powered for pCR; SOC pCR benchmark 56%; Target pCR Δ15% for both experimental arms
- Cap HR-negative patients at 30% (natural prevalence)
- N+ or large tumor only eligible

DESTINY-Breast05 Study Design

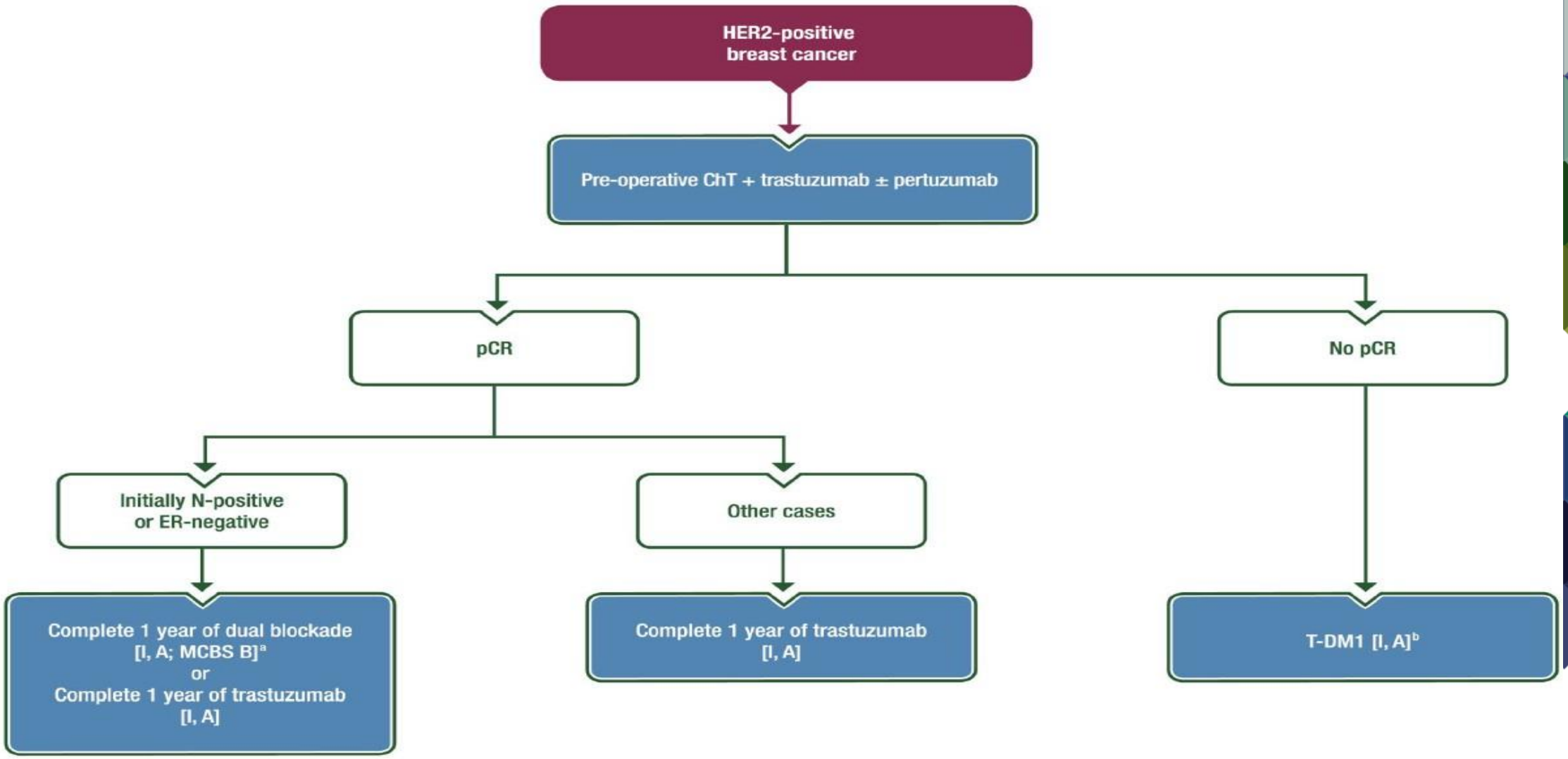


AE=adverse event; BMFI=Brain metastases-free interval; DFS=Disease-free survival; DRFI=Distant recurrence-free interval; eBC=early breast cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; FU=follow-up; HER2=Human epidermal growth factor receptor 2; IDFS=Invasive disease-free survival; OS=Overall survival; PK=pharmacokinetics; PRO=patient reported outcome; QoL=quality of life R=randomization

In coalition with Syneos Health



Cardoso F et al., ESMO Clinical Practice Guidelines for Early Breast Cancer



Cardoso F et al, Annals of Oncology 2019

CLINICAL PRACTICE GUIDELINES

(Neo)Adjuvant systemic treatment

Treatment choice by marker expression and intrinsic phenotype

(Neo)-adjuvant systemic treatment choice by marker expression and intrinsic phenotype.

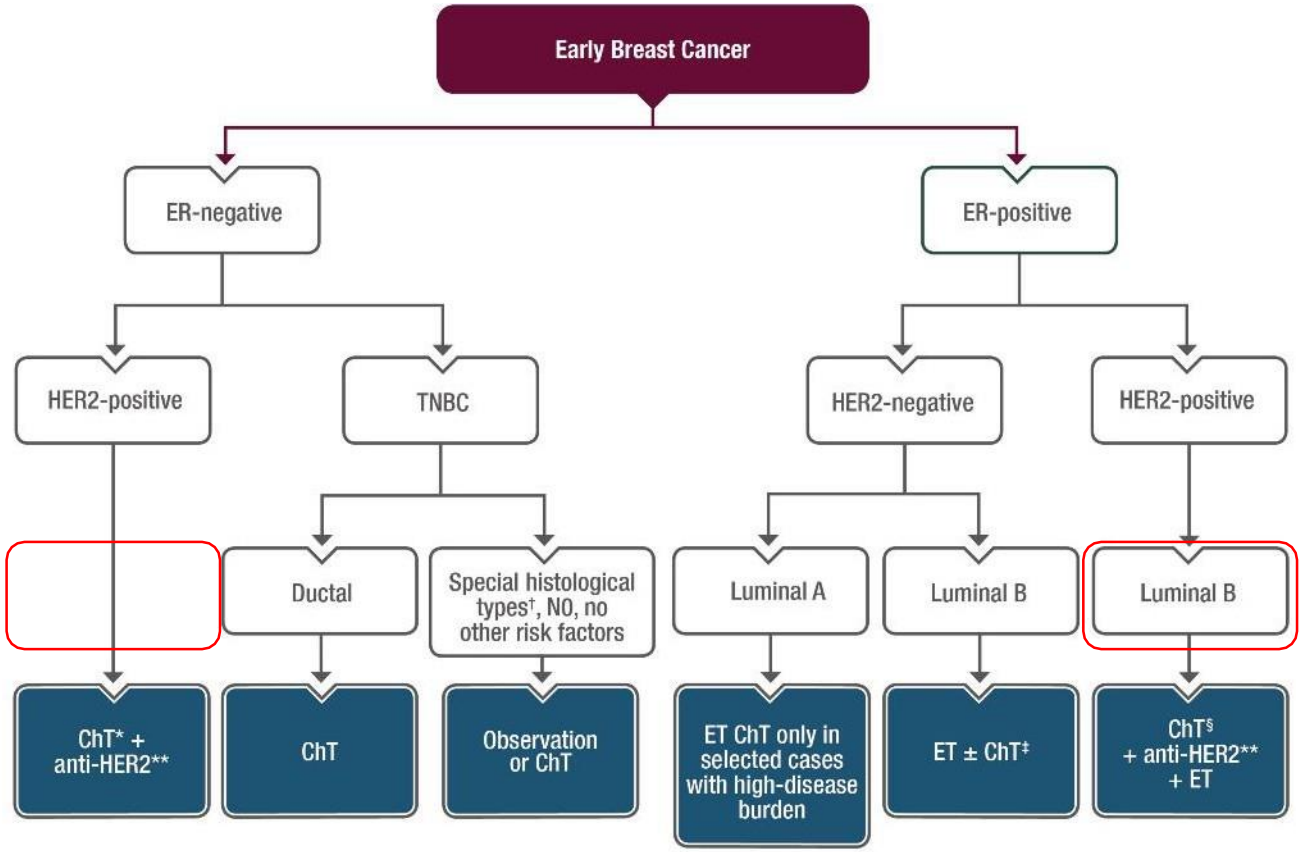
* With possible exception of selected cases with very low risk T1abN0.

** Anti-HER2: trastuzumab ± pertuzumab.

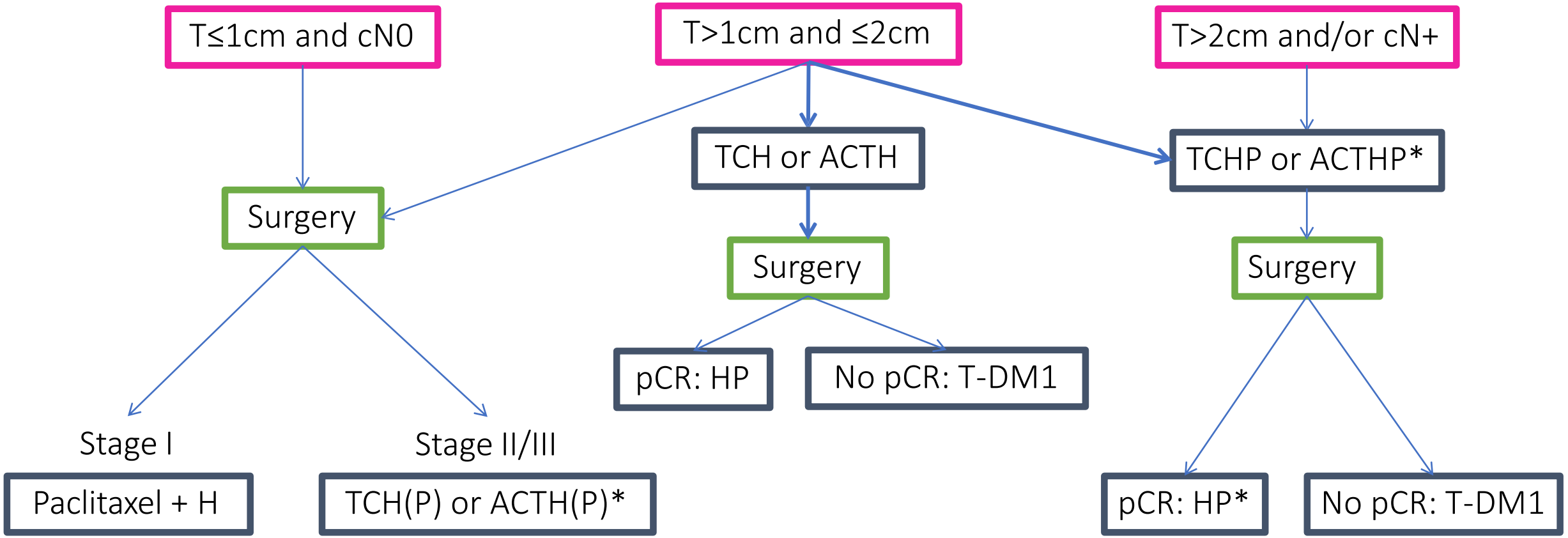
† Adenoid cystic or apocrine, secretory carcinoma, low-grade metaplastic carcinoma.

‡ Depending on level of ER and PgR expression, proliferation, genomically assessed risk, tumour burden and/or patient preference.

§ Except for very low-risk patients T1abN0 for whom ET/anti-HER2 therapy alone can be considered.



HER2-POSITIVE EBC MANAGEMENT ALGORITHM



*Depending on nodal status
pT1a pN0: paclitaxel + trastuzumab in HR-; for HR+, discuss case by case
pT1bc pN0: paclitaxel + trastuzumab

H = trastuzumab; P = pertuzumab; T-DM1 = trastuzumab-emtansine;
TCH = docetaxel/carboplatin/trastuzumab;
ACTH = doxorubicin/cyclophosphamide/paclitaxel/trastuzumab

Christos Sotiriou and Javier Cortes

Thank You