The Current Landscape and Future Direction of Neoadjuvant Therapy in Stage II-III HER2+ Breast Cancer

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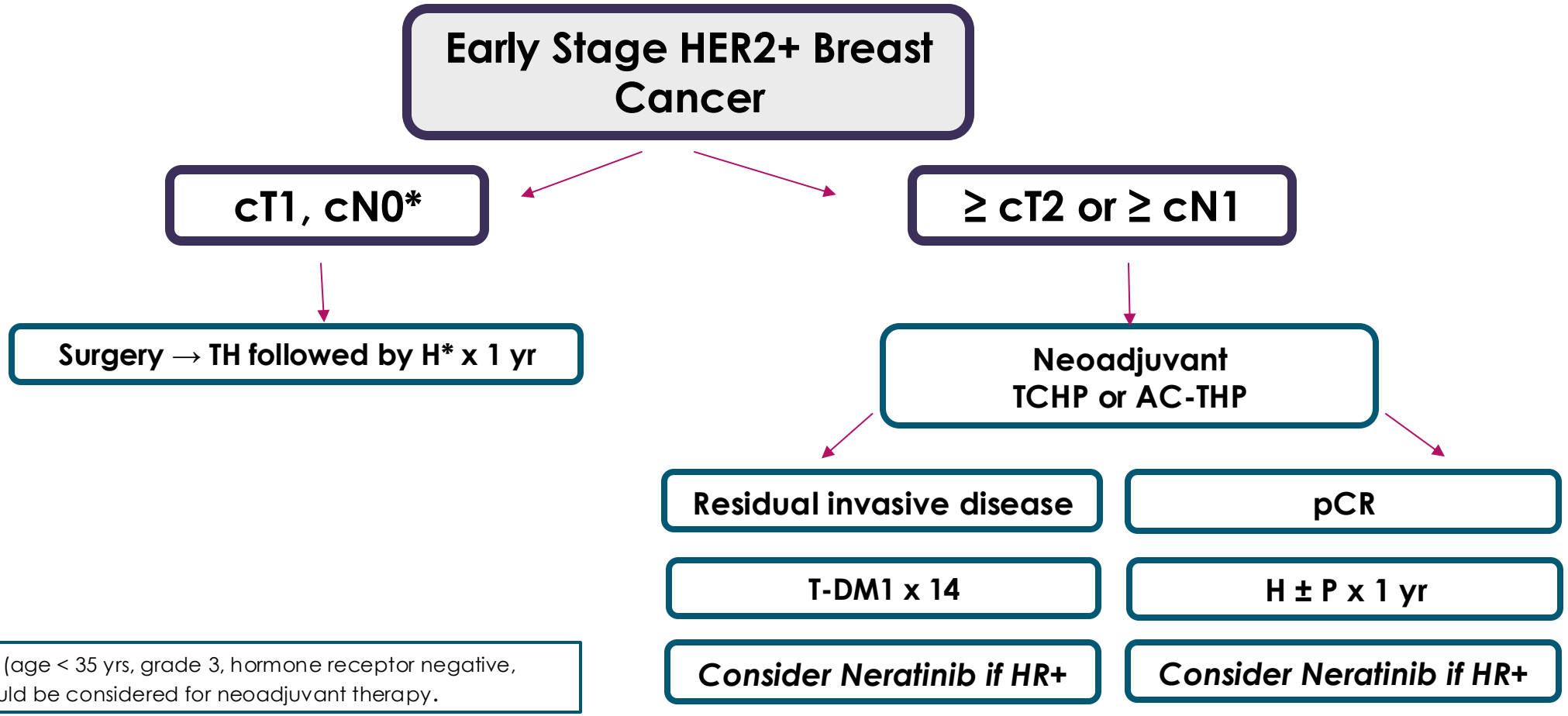
The University of Kansas Comprehensive Cancer Center

Current management of patients with early stage HER2+ breast cancer



**T1c:* High-risk patients (age < 35 yrs, grade 3, hormone receptor negative, multifocal disease) could be considered for neoadjuvant therapy.

Considerations in decision making for stage II- III HER2+ breast cancer

- Stage II-III disease
  - What is the role of anthracyclines?
  - Can we de-escalate neoadjuvant therapy in HER2+, early breast cancer?
  - Can we de-escalate following pCR to an abbreviated neoadjuvant regimen?
    - How abbreviated can that neoadjuvant regimen be?
  - Biomarkers: which are promising and how should we use them?
  - How should we escalate adjuvant therapy for those patients without pCR?

Is anthracycline-based chemotherapy necessary? NACT principles learned from BCIRG-006

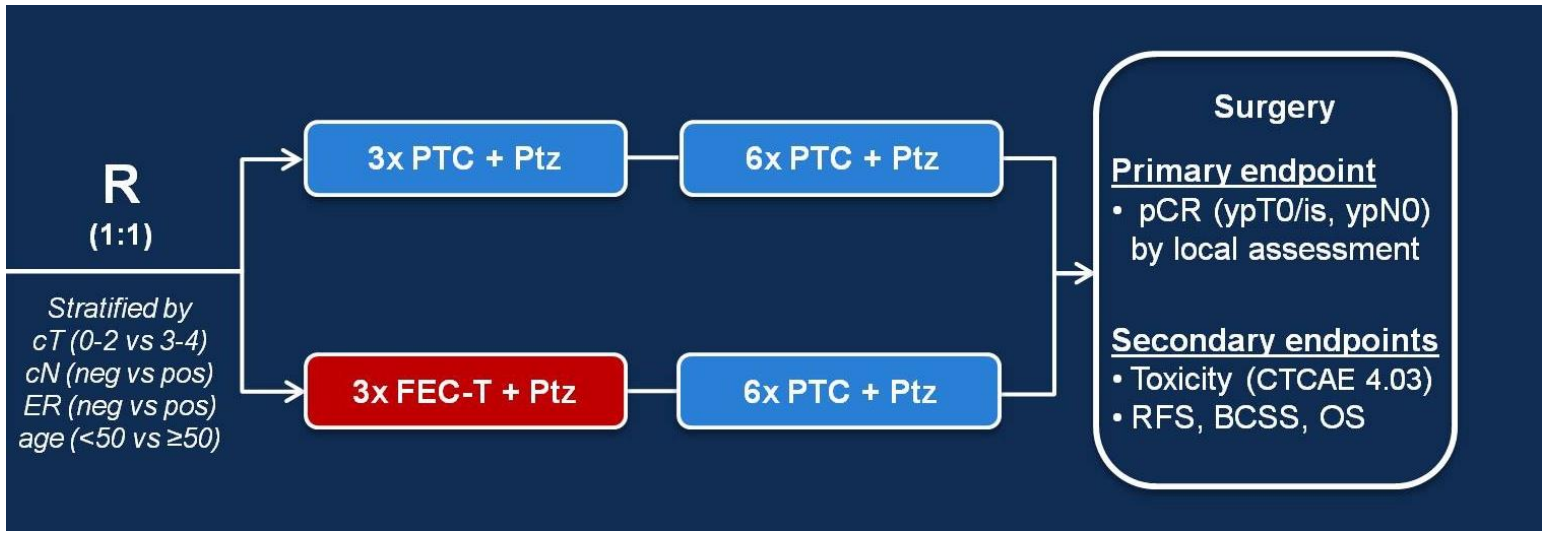
BCIRG006: 10.3 YRS FOLLOW-UP:

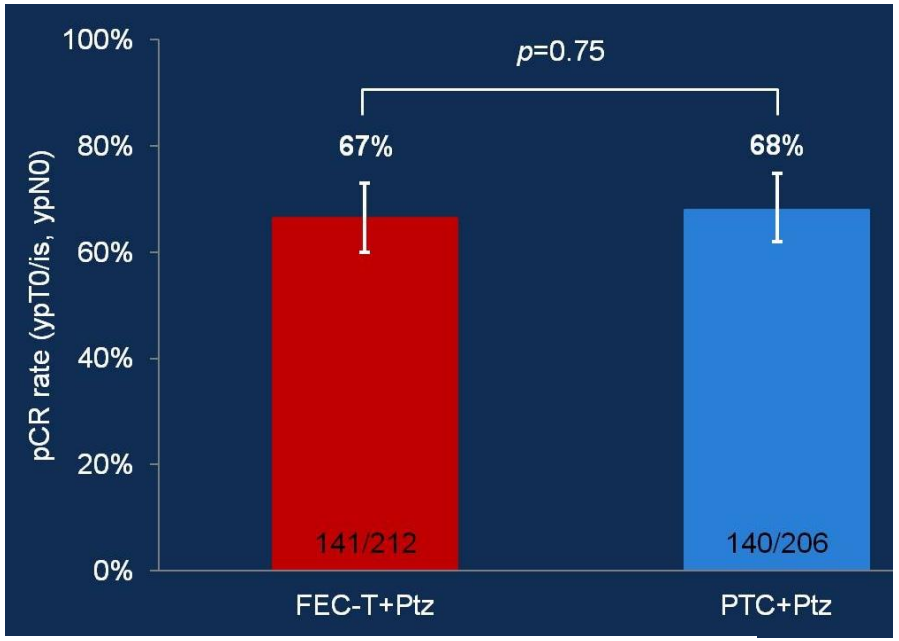
Outcome	AC → T (n = 1073)	AC → TH (n = 1074)	TCH (n = 1075)
DFS, % (n/N) HR (95% CI)	67.9 (328/1073) 1	74.6 (269/1074) 0.72 (0.61-0.85); *P* < .0001	73.0 (279/1075) 0.77 (0.65-0.90); *P* = .0011
OS, % (n/N) HR (95% CI)	78.7 (203/1073) 1	85.9 (141/1074) 0.63 (0.51-0.79); *P* < .0001	83.3 (167/1075) 0.76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

- **TCH ASSOCIATED WITH LESS CARDIAC TOXICITY (21 cases of grade 3 or 4 CHF in ACTH vs 4 in TCH, p=0.005) AND NUMERICALLY FEWER CASES OF SECONDARY LEUKEMIA (7 patients receiving anthracyclines, 1 in TCH group)**

Slamon D et al. SABCS 2015. Abstract S5-04.

TRAIN-2: Substituting anthracycline with taxane





- Stage II-III HER2+ breast cancer
- Neoadjuvant paclitaxel/carbo/HP x9 vs FEC/HP x3→paclitaxel/carbo/HP x6

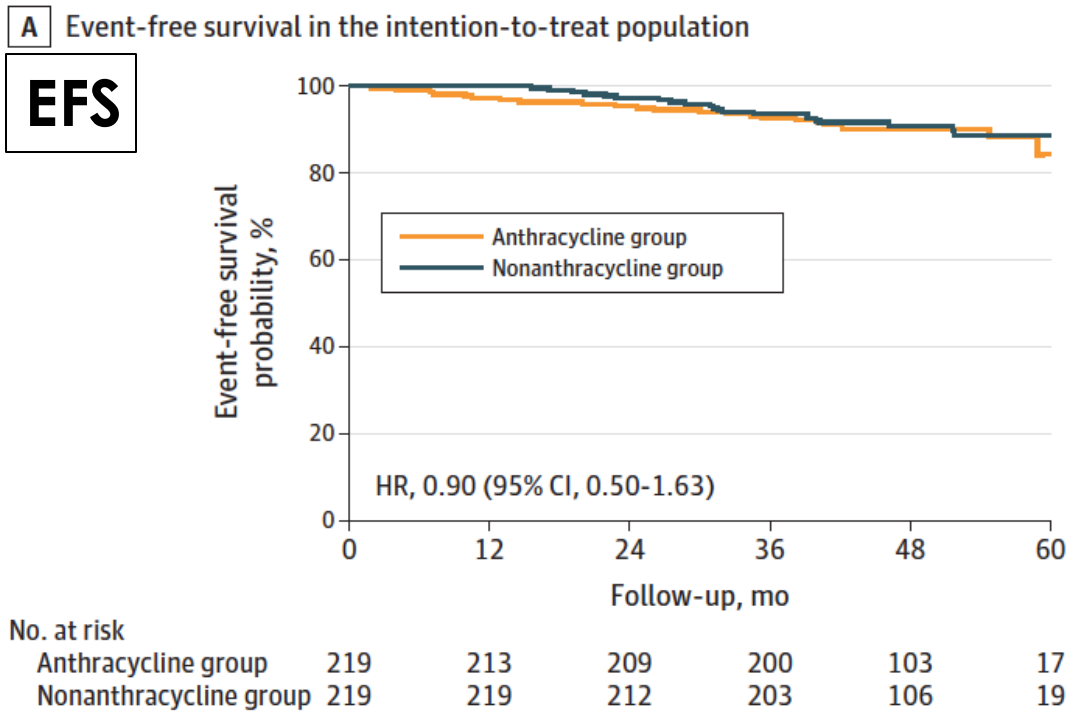
Van Ramshorst MS et al. ASCO 2017. Abstract 507; Lancet Oncol 2018;19(12):1630-1640.

TRAIN-2: EFS and OS are the same

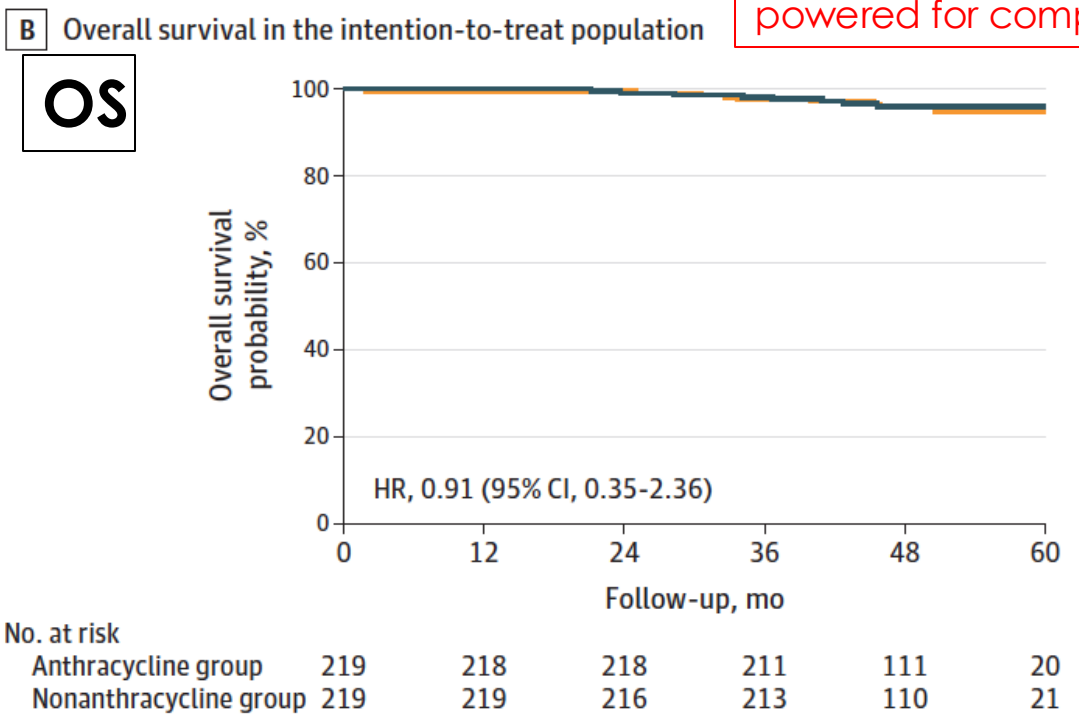
- *48.8 mos median f/u*

Secondary endpoints – not powered for comparison

EFS



OS



- Significantly less cardiac toxicity in non-FEC arm *(*concurrent anthracycline + HP)*
- 2 leukemia in FEC arm (vs 0 in non-FEC arm)

Van der Voort A et al JAMA Oncol 2021;7(7):978-984

TRAIN-2: EFS findings similar across all subgroups

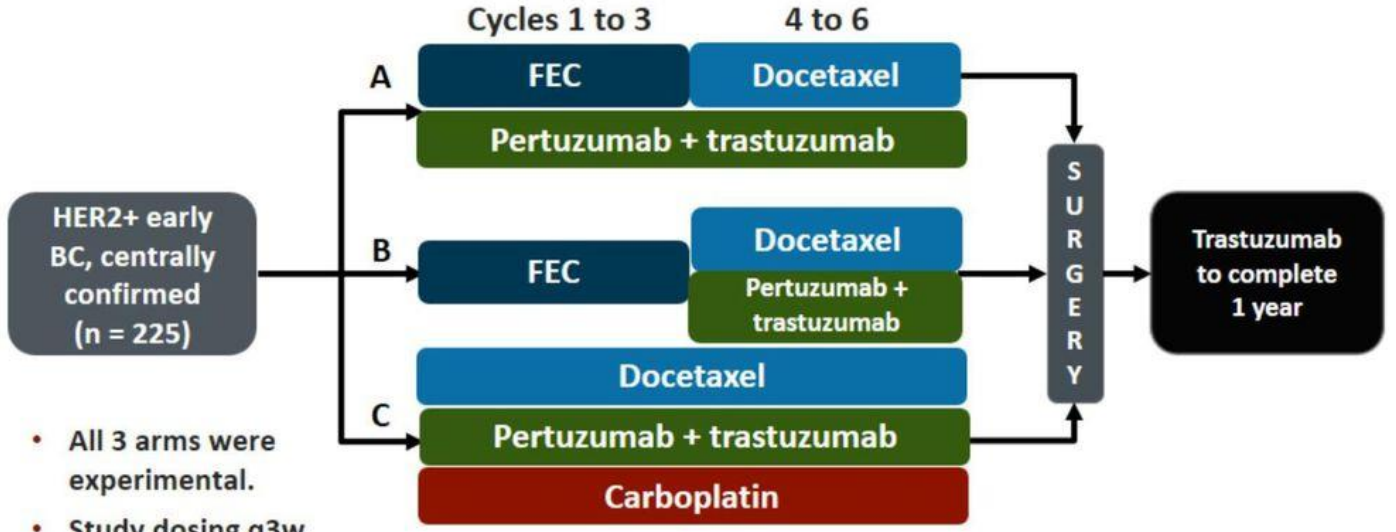
Subgroup	Patients, No./total No. (%) Nonanthracycline (n=219)	Anthracycline (n=219)	Hazard ratio (95% CI)[a]
Hormone receptor			
Positive	13/126 (10.3)	15/129 (11.6)	0.84 (0.40-1.77)
Negative	8/93 (8.6)	8/90 (8.9)	1.00 (0.38-2.68)
Age, y			
<50	10/118 (8.5)	10/119 (8.4)	1.04 (0.43-2.50)
≥50	11/101 (10.9)	13/100 (13.0)	0.80 (0.36-1.78)
Clinical tumor stage			
0-2	13/154 (8.4)	11/147 (7.5)	1.10 (0.49-2.45)
3-4	8/65 (12.3)	12/72 (16.7)	0.76 (0.31-1.87)
Clinical nodal status			
Negative	2/76 (2.6)	4/82 (4.9)	0.53 (0.10-2.90)
Positive	19/143 (13.3)	19/137 (13.9)	0.95 (0.50-1.79)
Disease stage			
II[b]	11/151 (7.3)	10/139 (7.2)	1.00 (0.42-2.35)
III	10/68 (14.7)	13/80 (16.3)	0.92 (0.40-2.09)
Tumor grade[c]			
1-2	11/113 (9.7)	16/107 (15.0)	0.63 (0.29-1.37)
3	8/95 (8.4)	7/101 (6.9)	1.23 (0.44-3.38)
All patients	21/219 (9.6)	23/219 (10.5)	0.90 (0.50-1.63)

Van der Voort A et al JAMA Oncol 2021;7(7):978-984

TRYPHAENA phase II clinical trial:

- pCR rate for TCHP 64% vs 55% with FEC-T with concurrent trastuzumab and pertuzumab
  - Not statistically significant and not powered for pCR rates

TRYPHAENA: Neoadjuvant Trastuzumab and Pertuzumab in HER2+ Early BC: Study Design (Phase 2)



- All 3 arms were experimental.
- Study dosing q3w
  - FEC: 500 mg/m^2, 100 mg/m^2, 600 mg/m^2
  - Carboplatin: AUC 6
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Pertuzumab: 840 mg loading dose, 420 mg maintenance
  - Docetaxel: 75 mg/m^2 (escalating to 100 mg/m^2 if tolerated, in arms A and B only)
- Stratification
  - Operable, locally advanced, and inflammatory BC
  - HR positivity

Schneeweiss A, et al. *Ann Oncol*. 2013;24:2278-2284.[19]

NeoSphere: multicenter, open-label, phase 2 randomized trial

- Primary analysis of NeoSphere:
  - 417 HER2+ patients randomized to receive 12 weeks of NAT:
    - Group A: trastuzumab plus docetaxel
    - Group B: HP + docetaxel
    - Group C: HP
    - Group: Pertuzumab plus docetaxel
  - After surgery, all patients completed 1 year of trastuzumab
  - Primary endpoint: pCR in the breast: **patients receiving docetaxel, pertuzumab, trastuzumab had higher pCR (46%)** vs docetaxel and trastuzumab (29%) or just pertuzumab (24%)
  - Secondary endpoints: clinical response rate, time to clinical response, breast conserving surgery rate, and safety
- At 5 years: PFS, DFS, and safety reported

NeoSphere PFS and DFS at 5 years

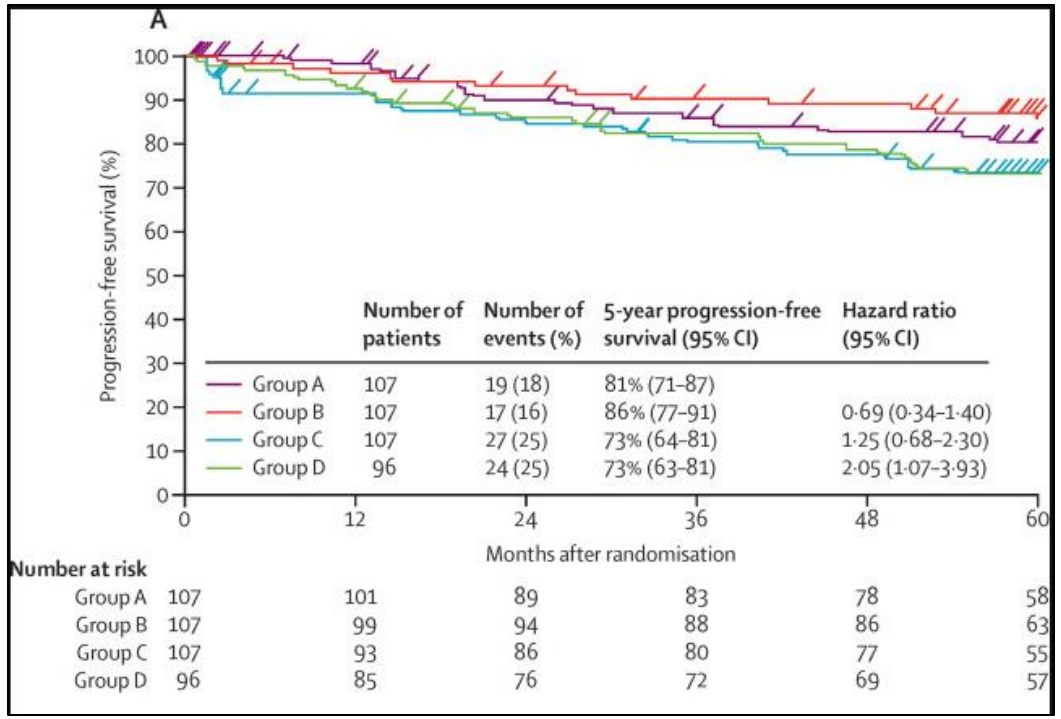


Figure 1A: Kaplan meier estimates of PFS in ITT

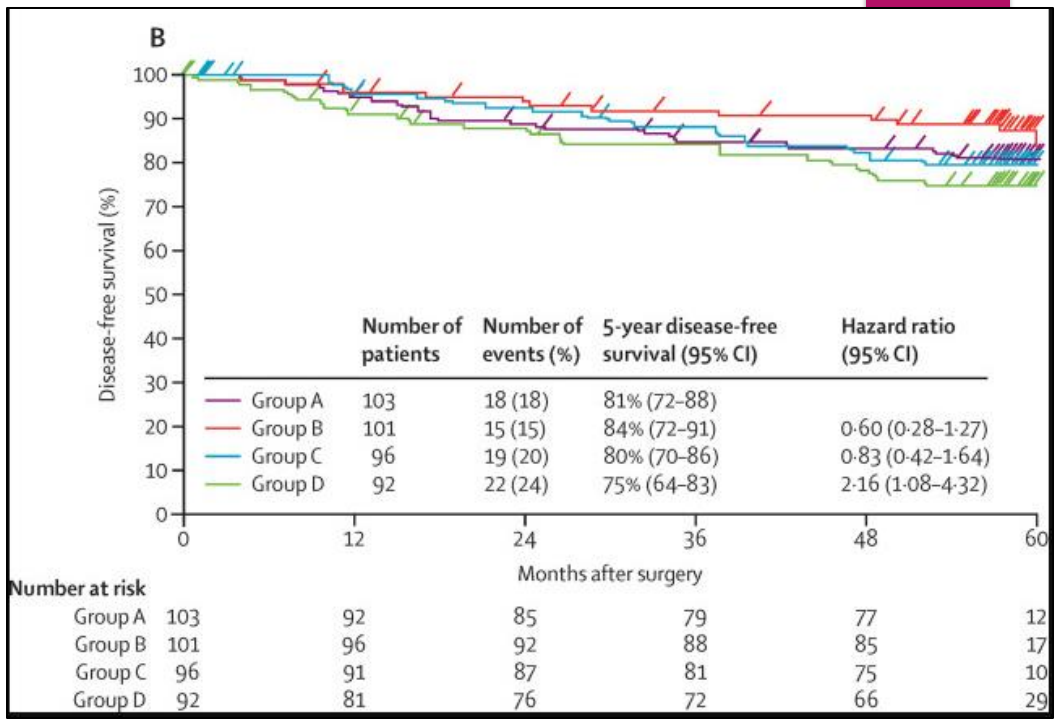


Figure 1B: Kaplan meier estimates of DFS in ITT

*Group A: trastuzumab plus docetaxel
*Group B: HP + docetaxel
*Group C: HP
*Group: Pertuzumab plus docetaxel

Summary: Anthracyclines can be substituted

- BCIRG006 and TRAIN-2 demonstrate similar long term outcomes with taxane-based therapy as with anthracycline-based therapy, even in high-risk node-positive patients
- TRYPHAENA and NeoSphere provide further data on safely avoiding anthracycline-based therapy in neo-adjuvant setting
- Less cardiac toxicity and numerically less leukemia

Considerations in decision making for stage II- III HER2+ breast cancer

- **Stage II-III disease**
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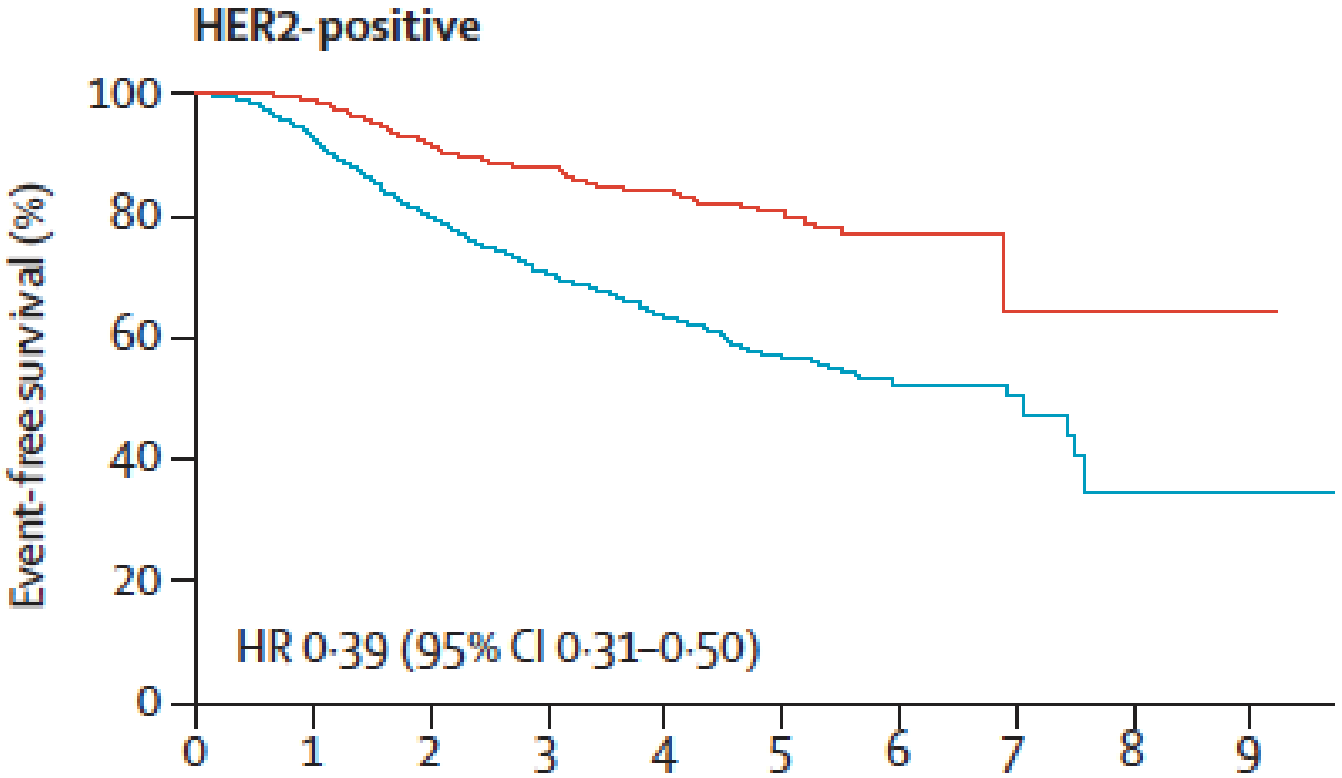
Treatment de-escalation

- Achieving pCR after NACT is a strong individual prognostic factor for HER2+ breast cancer
- Anti-tumor effect of NACT HER2-targeted therapy raises the question of chemotherapy de-escalation
  - Can we achieve similar pCR rates with less cytotoxic chemotherapy in HER2+, ER- early breast cancer?

pCR is a strong prognostic indicator on an individual level



pCR

Non-pCR

HR 0.39

Cortazar P et al Lancet 2014;384:164-172

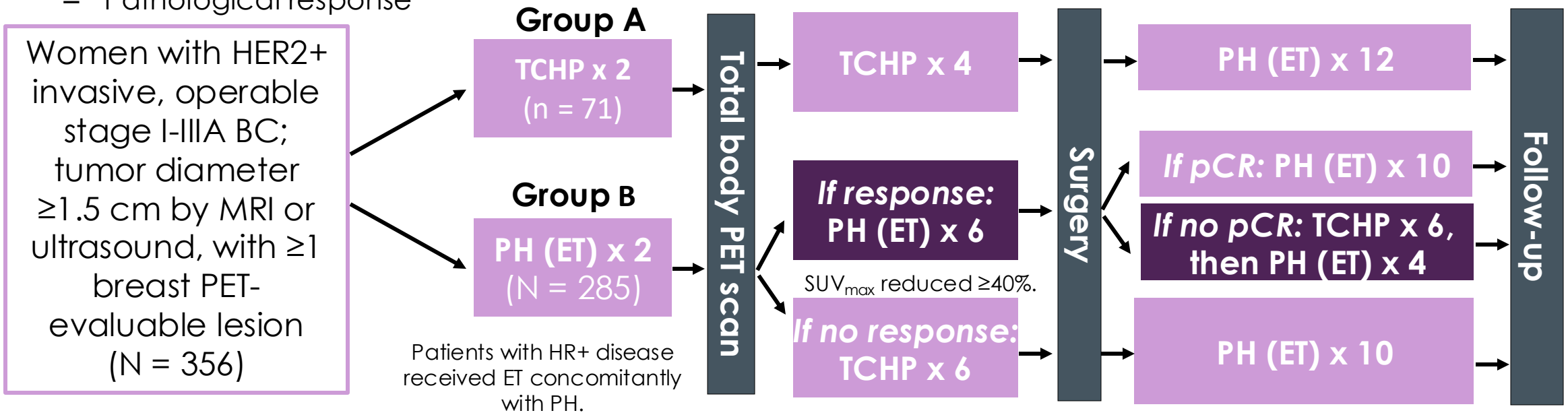
Exploratory analyses of de-escalation post-pCR in HER2+ breast cancer

Trial	Eligible pts	Abbreviated neoadjuvant regimen(s)	Abbreviated regimen: pCR rate (no. pts)	Adjuvant therapy post-pCR	Outcomes among pCR patients
KRISTINE	Stage IIA-IIIC	T-DM1+P x6 *(vs TCHP x6)*	44.4% (99 pts)	T-DM1 + P (all) Additional chemo (9.1%)	96.7% 3 yr iDFS
PHERGain	Stage I-IIIA (T size ≥1.5 cm)	HP x8 (+ET if HR+) **if classified as a responder by PET after first 2 cycles (80% of pts)*	37.9% (86 pts)	HP only (all) Additional chemo (TBD – 0% per protocol)	TBD (co-primary endpoint)
WSG-ADAPT-HER2+/HR-	Stage I-III ER and PR <1%	HP x4	34.4% (31 pts)	HP (all) Additional chemo (71%)	1 iDFS event at 5 yrs
WSG-ADAPT-HER2+/HR-	Stage I-III ER and PR <1%	THP x4 (T=paclitaxel)	90.5% (38 pts)	HP (all) Additional chemo (21%)	1 iDFS event at 5 yrs
DAPHNe	Stage II-III	THP x4 (T=paclitaxel)	56.7% (55 pts)	HP (all) Additional chemo (1.8%)	0 EFS events at 19 mos

Waks AG et al. NPJ Breast Cancer. 2022;8(1):63.; Nitz U et al. Lancet Oncol. 2022;23(5):625-635; Hurvitz et al. Lancet Oncol. 2018; 19(1):115-126; Perez-Garcia JM et al. Lancet Oncol. 2021;22(6):858-871.

PHERGain

- Multicenter, randomized, open-label, noncomparative phase II trial.
- Chemotherapy de-escalation in HER2+ early BC with a response-adaptive strategy based on:
  - Early metabolic response by PET-CT to neoadjuvant HP
  - Pathological response



Primary endpoints: pCR in PET responders (group B), **3-yr iDFS (group B)**

Stratified by HR status (+ vs -)

Cortes. ASCO 2023. Abstr LBA506

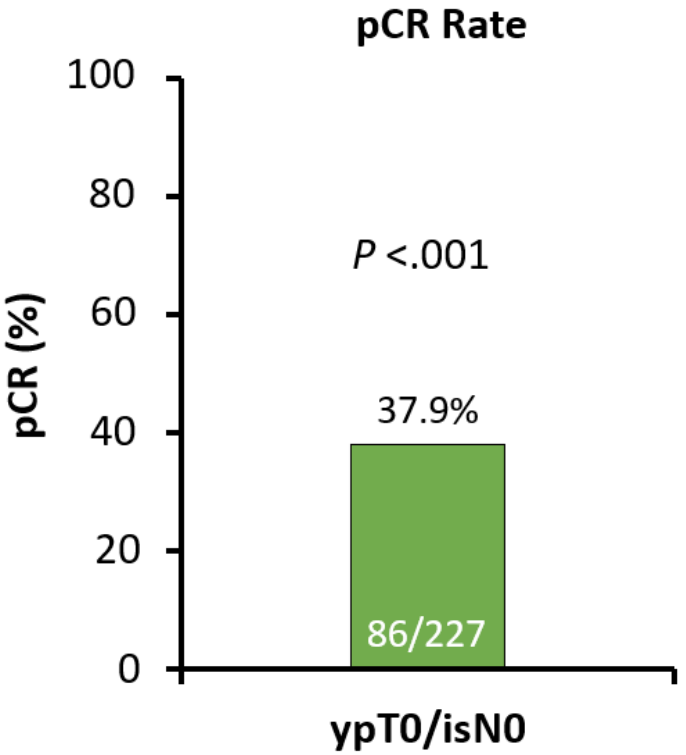
PHERGain: baseline characteristics

Characteristic, n (%)	Group A (n = 71)	Group B (n = 285)
Premenopausal/postmenopausal	37 (52.1)/34 (47.9)	146 (51.2)/139 (48.8)
ECOG PS 0/1	69 (97.2)/2 (2.8)	264 (92.6)/21 (7.4)
Unifocal disease	56 (78.9)	217 (76.1)
Stage		
▪ I	9 (12.7)	24 (8.4)
▪ II	50 (70.4)	219 (76.8)
▪ III	12 (16.9)	42 (14.7)
Node positive/node negative	32 (45.2)/39 (54.9)	140 (49.1)/145 (50.9)
HR status		
▪ ER- and PR-	27 (38.1)	93 (32.6)
▪ ER+ and/or PR+	44 (61.9)	192 (67.4)
HER2 status		
▪ IHC 2+ and FISH+	13 (18.3)	64 (22.5)
▪ IHC 3+	58 (81.7)	221 (77.5)

Cortes. ASCO 2023. Abstr LBA506.

PHERGain: pCR in PET responders in group B (primary endpoint)

- 227 (79.6%) patients in group B were PET responders and received only PH prior to surgery
- Following surgery, pCR in group B responders was 37.9%, exceeding null hypothesis (≤20%)
- pCR observed across patient subgroups
  - HER2+ IHC 2+ and 3+
  - Stage II and III
  - ER+ and ER-



Cortes. ASCO 2023. Abstr LBA506.

PHERGain: 3-year iDFS group B

- 3-yr iDFS rate: 95.4% (95% CI: 92.8-98%)
  - Events: 12/267
- Treatment group B met the second co-primary endpoint with ≤15 patients with iDFS events (*P* <.001)

3-Yr iDFS, n (%)	Group B (n = 267)
iDFS events	12 (4.5)
▪ Relapse	11 (4.1)
– Ipsilateral invasive BC recurrence	1 (0.4)
– Regional invasive BC recurrence	2 (0.8)
– Contralateral invasive BC	0 (0)
– Distant recurrence	8 (3.0)
▪ Nonrelated death without recurrence	1 (0.4)

Cortes. ASCO 2023. Abstr LBA506.

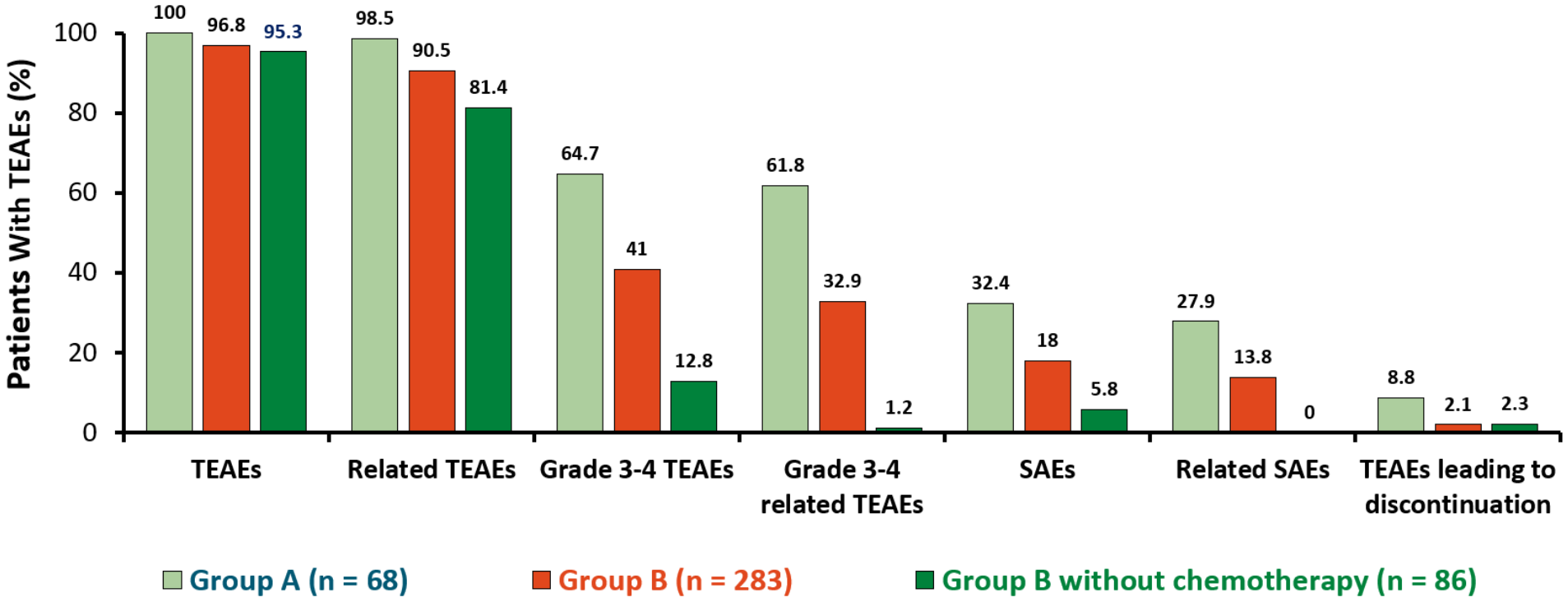
Efficacy (key secondary endpoints)

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

*Defined from time of surgery. †Defined from randomization.

Cortes. ASCO 2023. Abstr LBA506.

PHERGain: Safety data



- There were no deaths related to study treatment

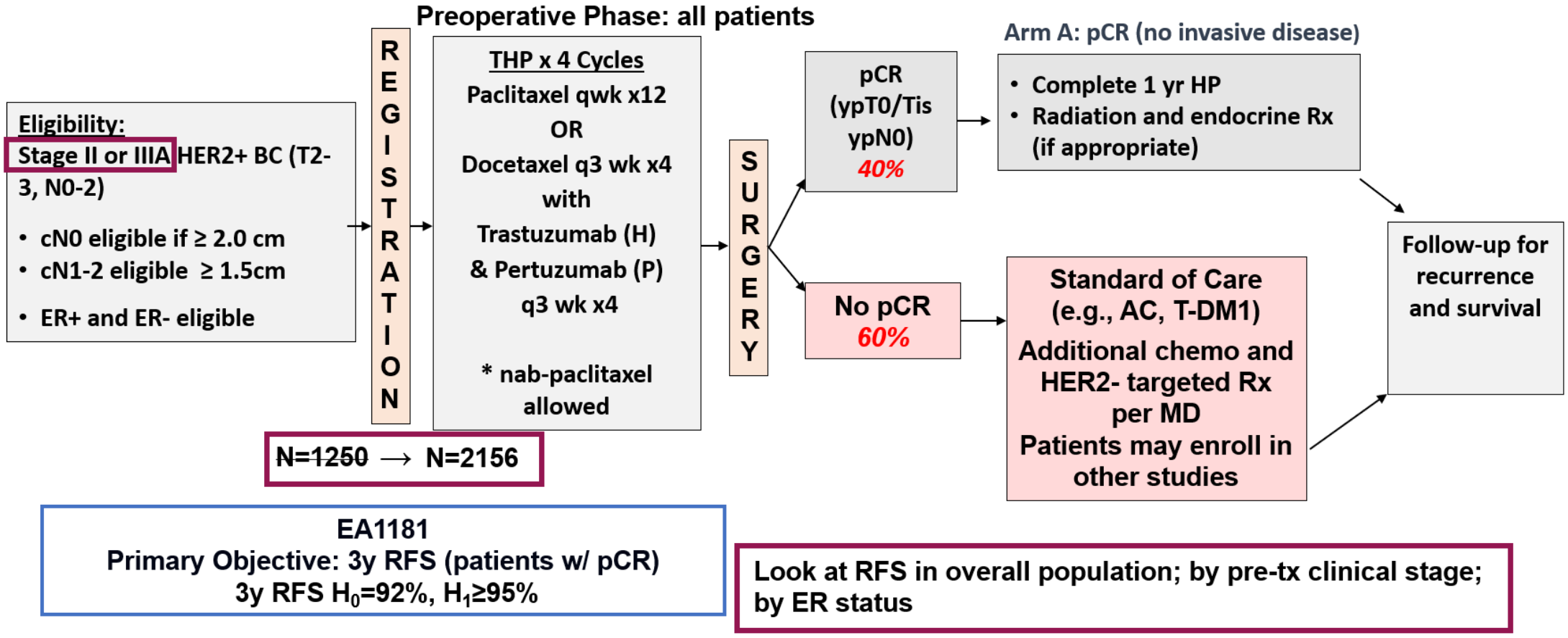
Cortes. ASCO 2023. Abstr LBA506.

Authors conclusions

- The PHERGain trial met its second primary endpoint with a 3-yr iDFS of 95.4% in group B.
  - 3-yr iDFS was 98.8% among patients with PET response and pCR treated with pertuzumab/trastuzumab and no chemotherapy.
- No expected safety signals.
- PET-based, response-adapted strategy identifies approximately 1 in 3 patients with HER2+ EBC who can safely omit chemotherapy and thereby significantly reduce toxicity.

Cortes. ASCO 2023. Abstr LBA506.

CompassHER2-pCR trial (ECOG/ACRIN 1181)



Activation Feb 2020, accrual complete

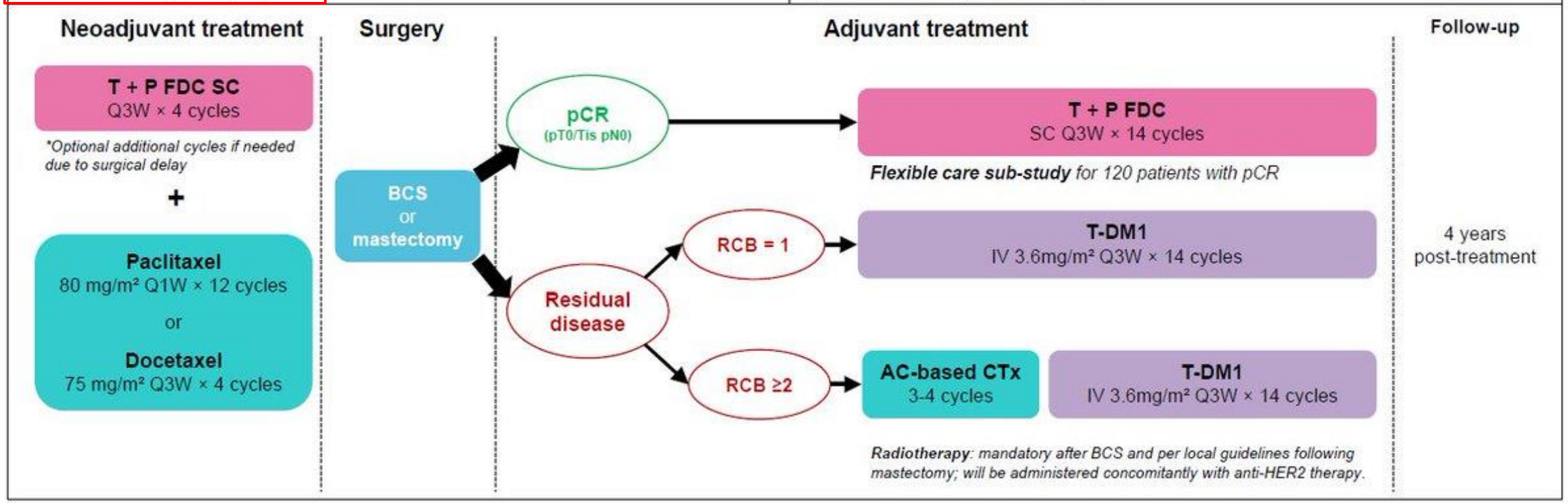
DECRESCENDO Study Design

*HER2+/**HR-** patients only

Patients (N=1065)
HER2-positive HR-negative invasive non-metastatic BC
Tumor size: ≥15mm and ≤50mm
Nodal status: negative (N0)

Stage I-IIA

1° endpoint
3-year RFS in 500 patients with pCR, HER2-enriched intrinsic subtype
Key 2° endpoint (hierarchical testing)
3-year RFS in all patients with pCR



AC: anthracycline; **BC:** breast cancer; **BSC:** breast-conserving surgery; **CTx:** chemotherapy; **HER2:** human epidermal growth factor receptor-2; **HR:** hormone receptor; **IV:** administered by intravenous injection; **pCR:** pathological complete response; **Q1W:** every week; **Q3W:** every 3 weeks; **RCB:** residual cancer burden score; **RFS:** relapse-free survival; **SC:** administered by subcutaneous injection; **T-DM1:** trastuzumab emtansine; **T + P FDC:** trastuzumab + pertuzumab fixed-dose combination

DECRESCENDO breast cancer trial

Currently enrolling

Conclusions: De-escalation in stage II-III disease

- COMPASSHER2-pCR and DECRESCENDO will provide info on efficacy of neoadjuvant THP (although stage III disease may not be well represented)
- Optimal management for the non-pCR patients will still be remaining question
- There is probably a subset of patients who only need HP
  - Or an alternative non-chemo regimen(s)
  - How do we best identify them early on?