

Neoadjuvant therapy of early stage HER2-positive breast cancer : Latest evidence and clinical implications

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Contents in today's talk

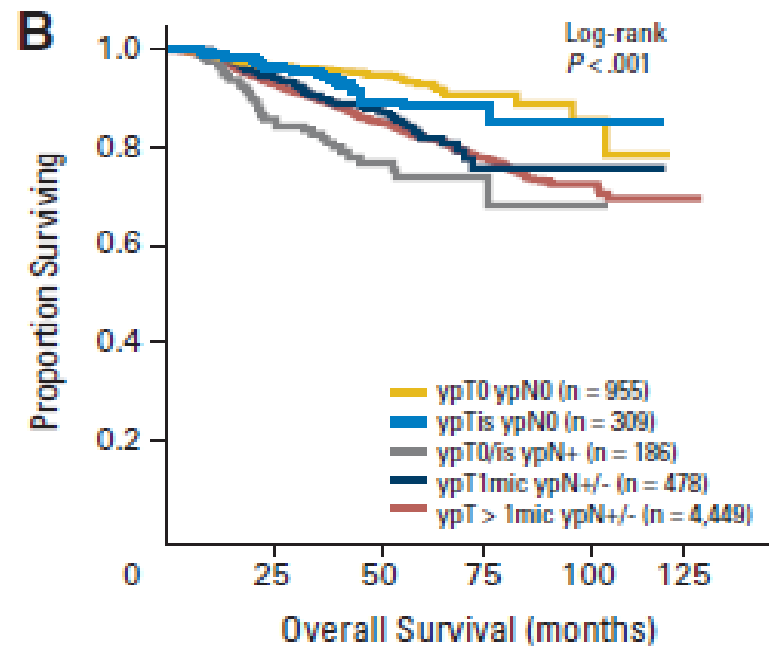
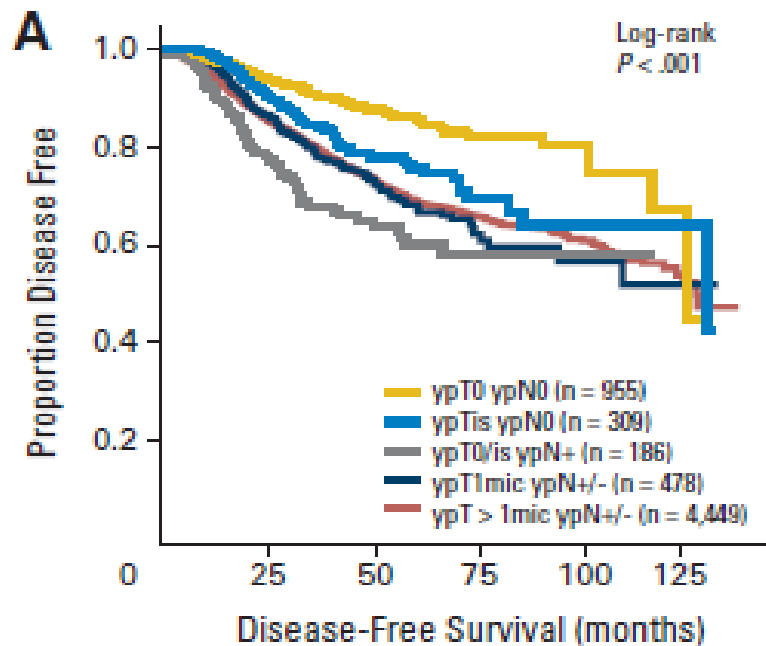
- **Rationale for neoadjuvant chemotherapy**
- **Clinical implications of pCR**
- **Anti-HER2 agents for HER2 positive breast cancer in neoadjuvant setting**
 - ✓ **Trastuzumab**
 - ✓ **Lapatinib**
 - ✓ **Pertuzumab**
 - ✓ **Others**
- **Ongoing trials**

Rationale for Neoadjuvant chemotherapy

- Early introduction of therapy for distant micrometastatic disease
- Convert inoperable to operable tumor
- Breast conserving strategy
- No disadvantage for neoadjuvant therapy compared with classical adjuvant therapy (**NSABP B-18**)
- Obtain information on drug response and biomarker changes
 - accelerate drug approval

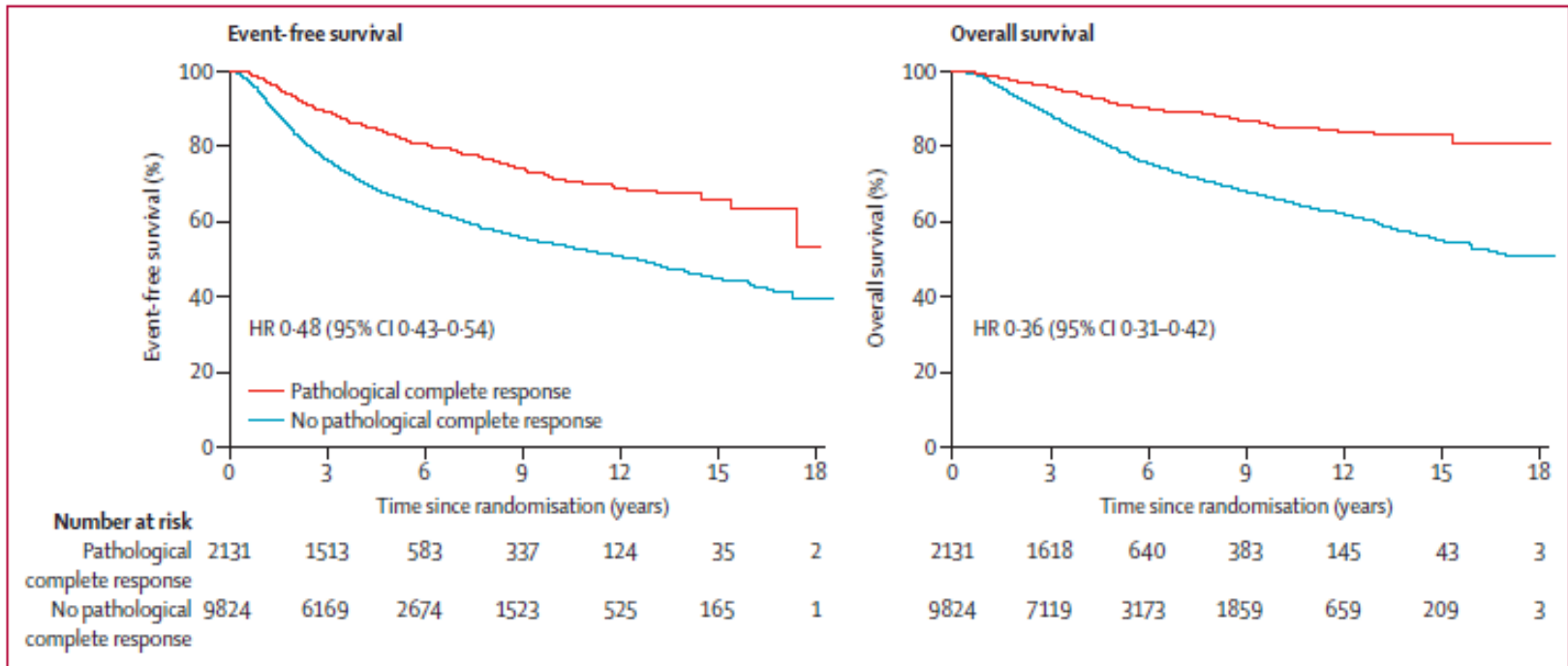
Pathologic complete response (pCR) : Definition and prognostic implication

7 randomized clinical trials, N= 6,377 patients
Anthracycline – taxane based chemotherapy

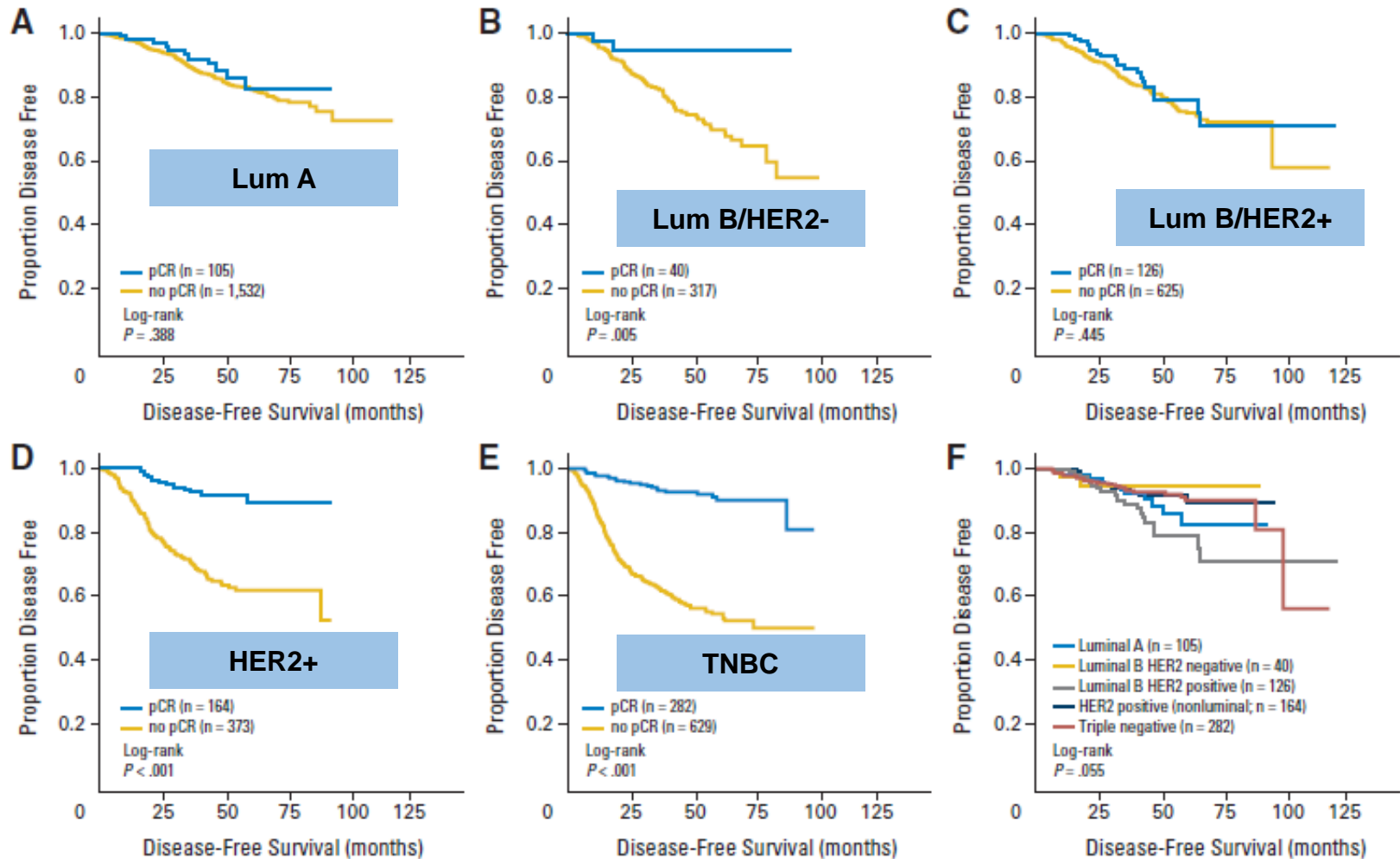


pCR and long term clinical benefit : the CTNeoBC pooled analysis

12 international clinical trials, N= 11,955 patients
Anthracycline – taxane based chemotherapy



Clinical impact of pCR according to subtypes



Interaction of trastuzumab and clinical impacts of pCR

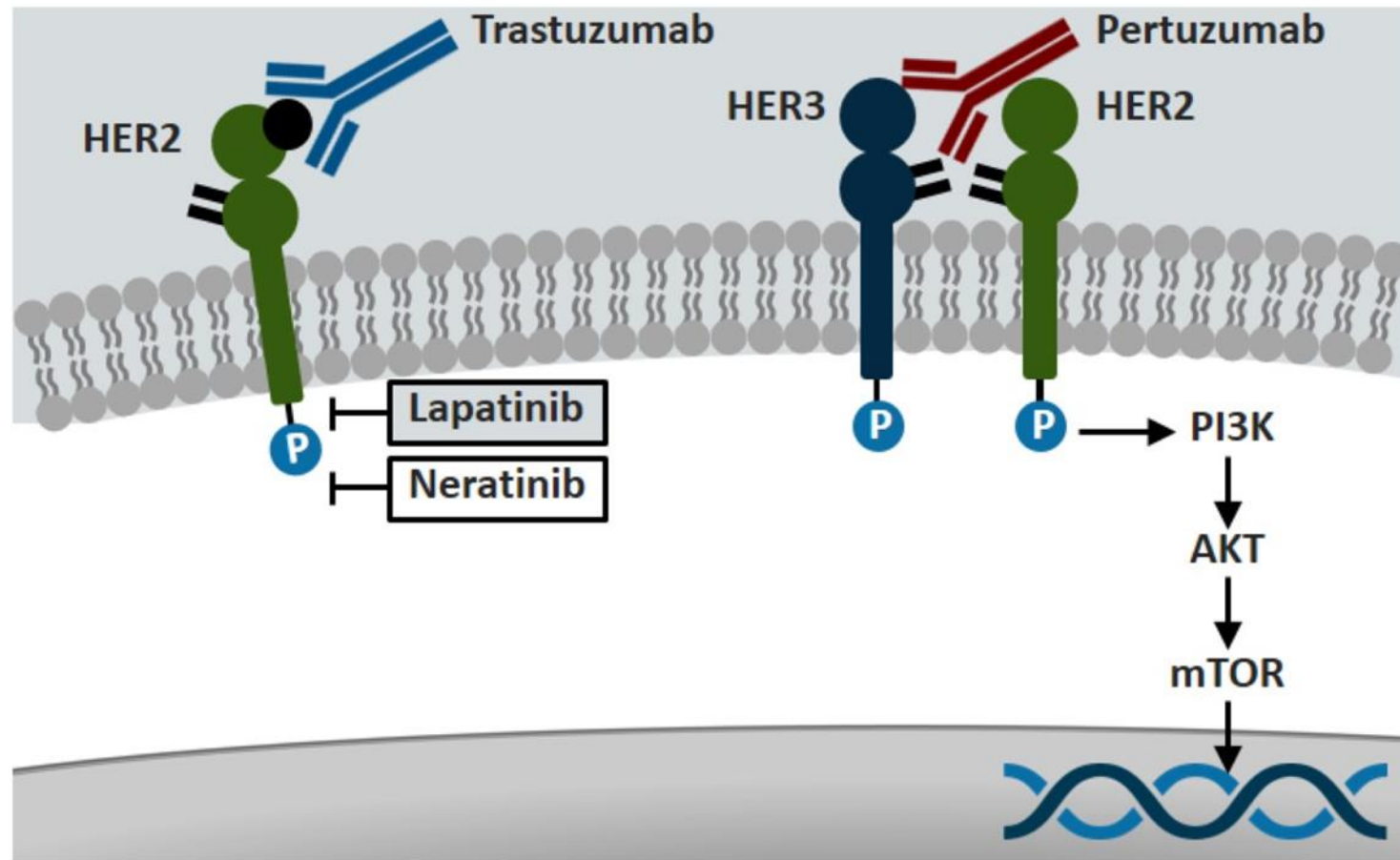
Von Minckwitz et al.

Subtypes	DFS ; HR (95% CI)	P-value
LumB/HER2+ without trastuzumab (N=395)	1.18 (0.59-2.36)	0.64
LumB/HER2+ with trastuzumab (N=356)	1.23 (0.63-2.37)	0.54
HER2+ without trastuzumab (N=239)	3.95 (1.89-8.28)	<0.001
HER2+ with trastuzumab (N=298)	8.74 (3.17-24.12)	<0.001

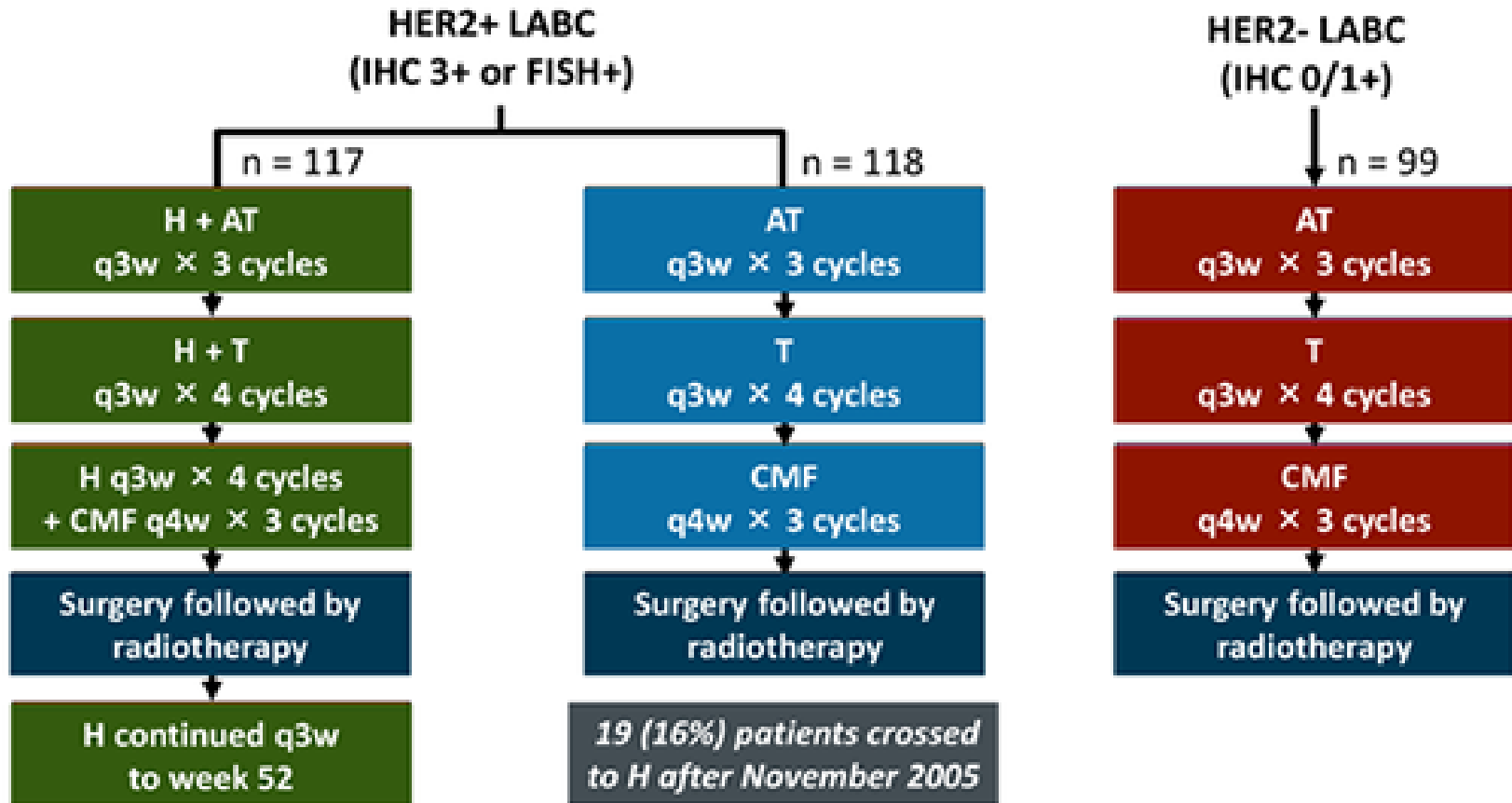
CTNeoBC analysis

Subtypes	pCR ; HR (95% CI)	OS ; HR (95% CI)
LumB/HER2+ without trastuzumab (N=701)	18.3 (15.5-21.3)	0.57 (0.31-1.04)
LumB/HER2+ with trastuzumab (N=385)	30.9 (26.3-35.8)	0.56 (0.23-1.37)
HER2+ without trastuzumab (N=471)	30.2 (26.0-34.5)	0.29 (0.17-0.50)
HER2+ with trastuzumab (N=364)	50.3 (45.0-55.5)	0.08 (0.03-0.22)

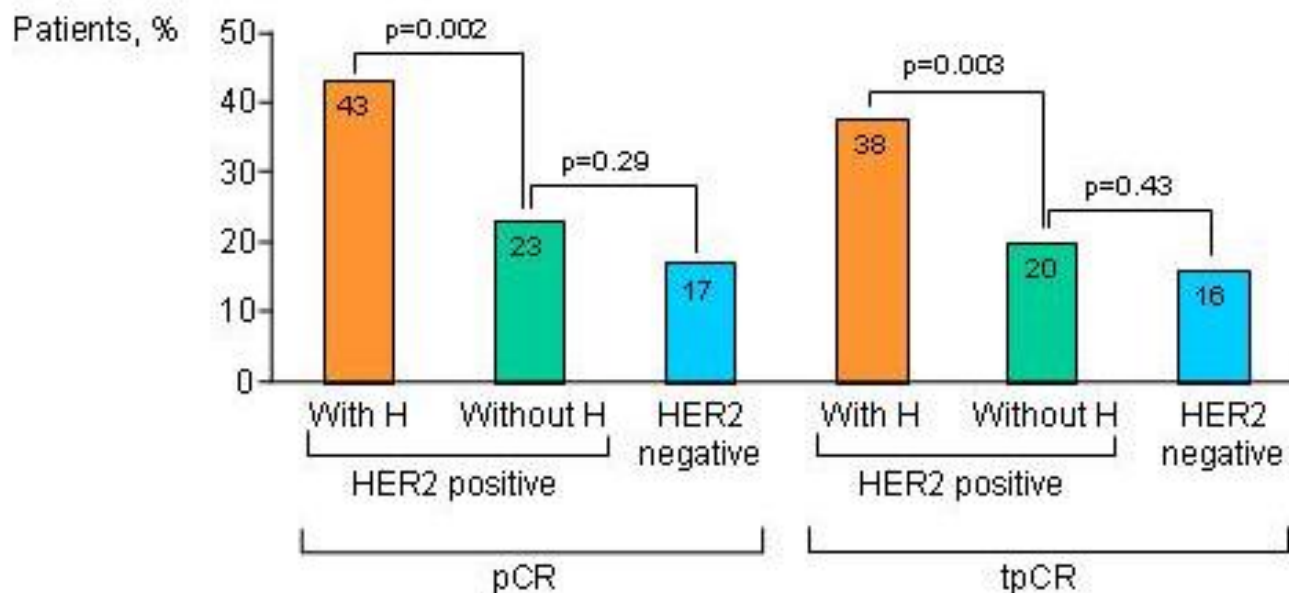
Targeted therapy in HER2 positive breast cancer



NOAH : phase III, open label trial of neoadjuvant trastuzumab



Cooperation of trastuzumab increased pCR & EFS : NOAH trial







	With T	Without T
N	117	118
Events	49 (41.9%)	62 (52.5%)
HR (95% CI)	0.64 (0.44-0.93)	
P-value	0.016	

Neoadjuvant trials with trastuzumab

	Regimen	pCR (%)	P-value
TECHNO (n=217)	ED → TH	39%	NR
MDACC (n=42)	T → FEC TH → FEC/H	26 65.2	0.016
NOAH (n=235)	AT → T → CMF AT/H → TH → CMF/H	22 43	0.0007
GEPAR-QUATTRO (N=445)	EC/H → DH EC/H → DXH EC/H → DH → XH	32.9 31.3 34.6	NR
GEPAR-QUINTO (N=620)	EC/H → DH EC/L → DL	30.3 22.7	0.04

Single vs. dual HER2 blockade : Lapatinib

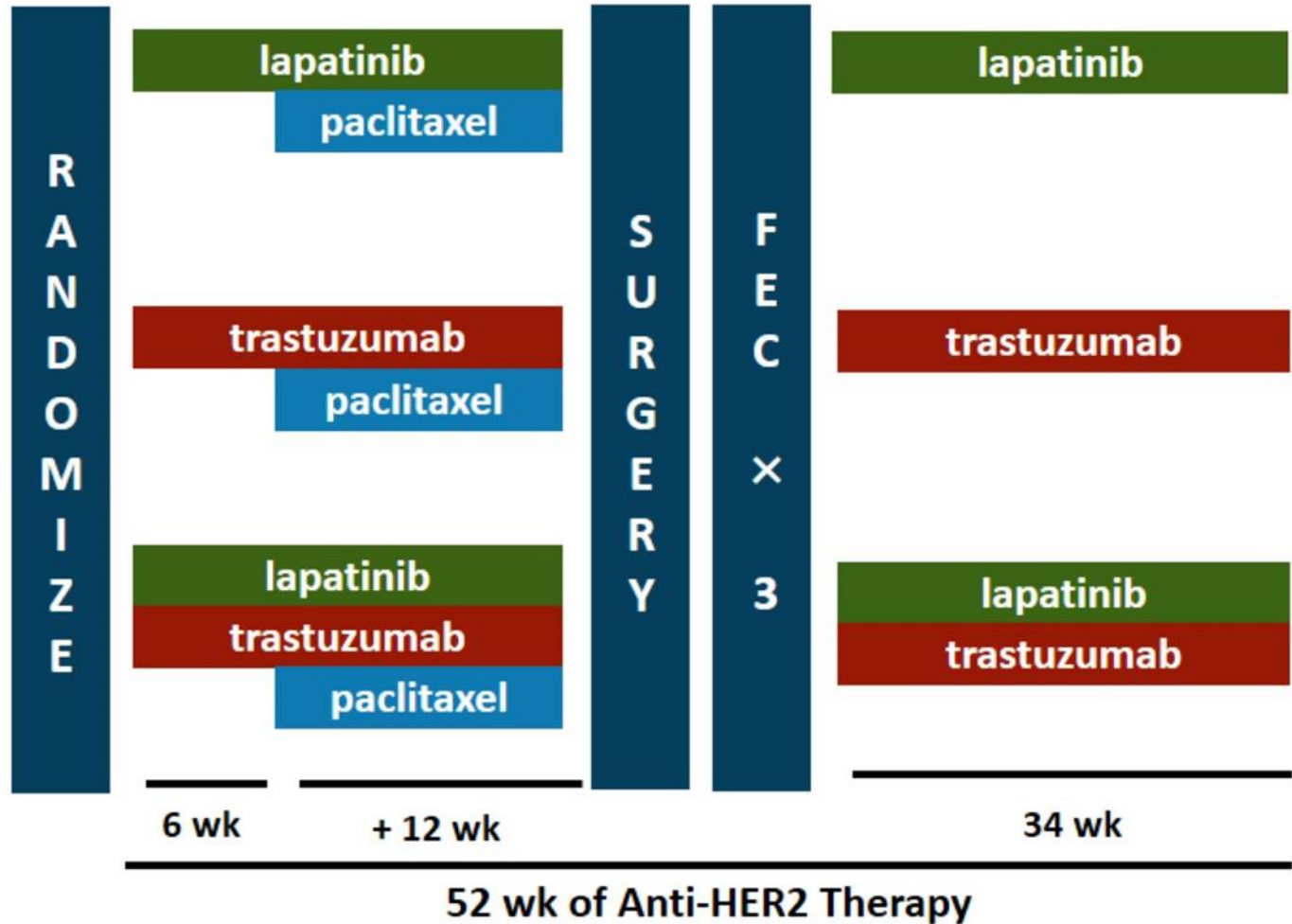
	Regimen	Duration, wk	pCR, %	P-value
NSABP B-41 (n=529)	AC → TH	28	52.5	0.095
	AC → TL		53.2	
	AC → THL		62 	
NeoALTTO (n=455)	TH	18	29.5	0.0001
	TL		24.7	
	THL		51.3 	
CHERLOB (n=121)	TH → FEC/H	24	25	0.19
	TL → FEC/L		26.3	
	THL → FEC/HL		46.7 	
CALGB40601 (n=235)	TH	16	46	0.12
	THL		56 	

NeoALTTO : dual HER2 blockade with lapatinib/trastuzumab

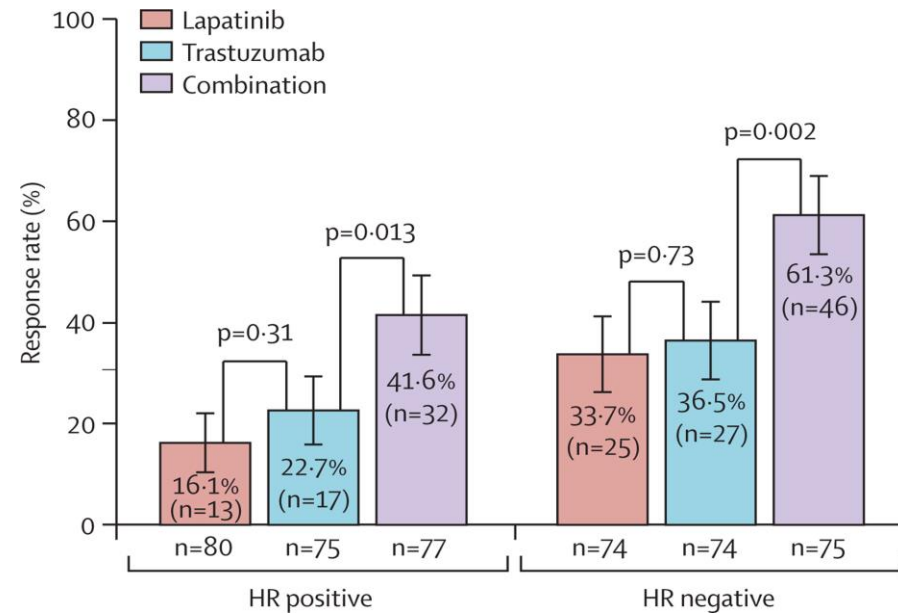
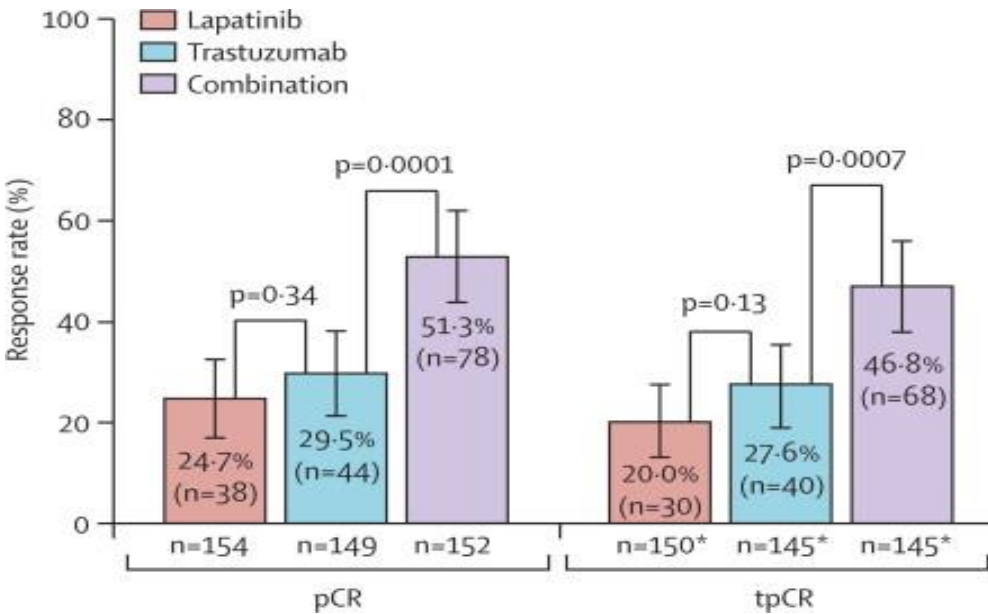
Invasive operable
HER2+ BC
Tumor > 2 cm
(inflammatory BC
excluded)
LVEF ≥ 50%
N = 450

Stratification

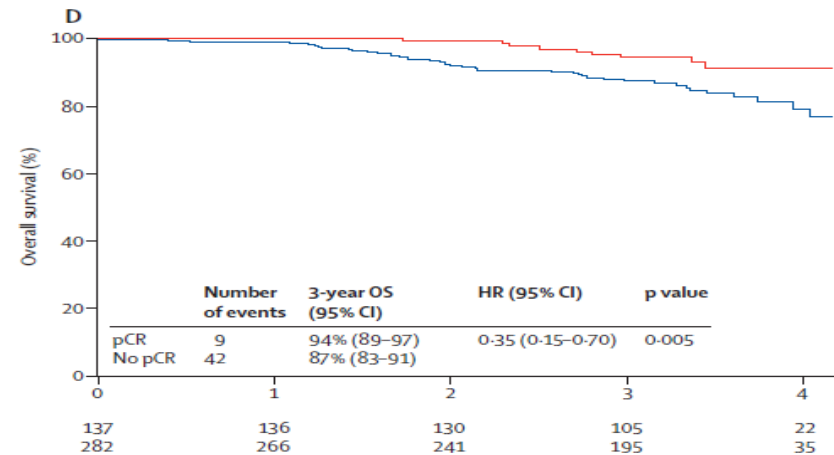
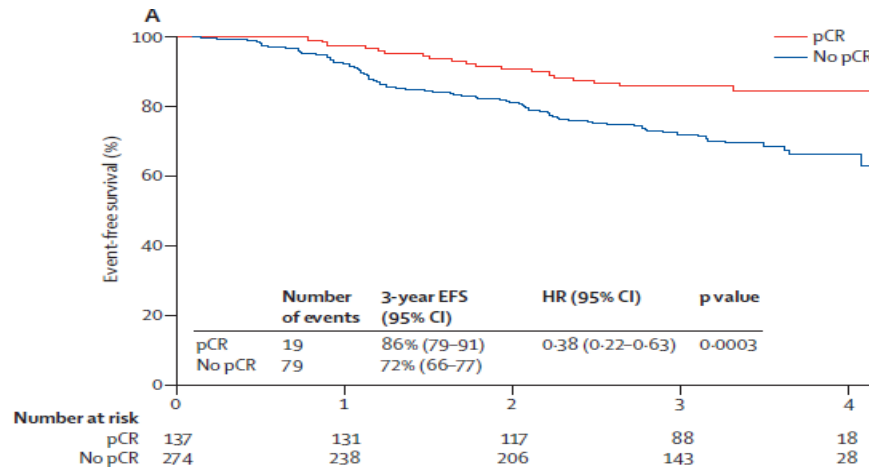
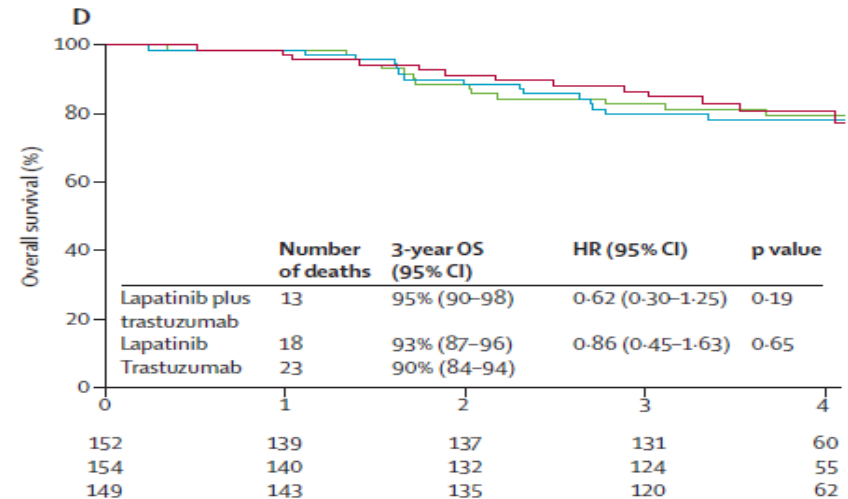
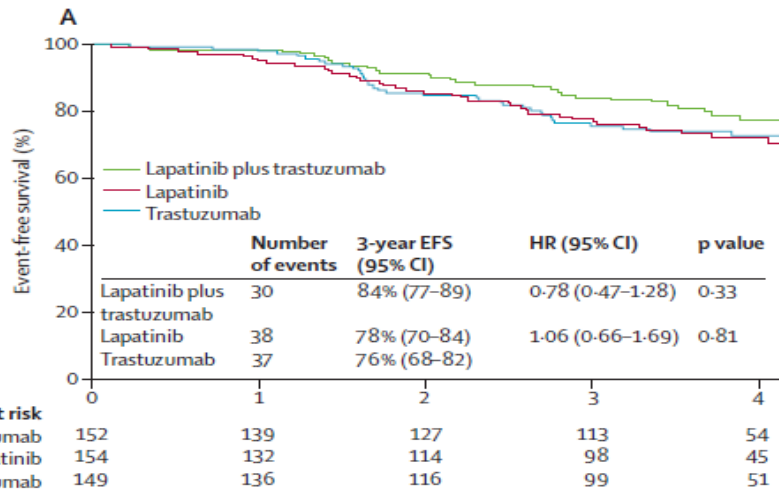
- Tumor ≤ 5 cm vs Tumor > 5 cm
- ER- or PgR+ vs ER- and PgR-
- N 0-1 vs N ≥ 2
- Conservative surgery or not



Lapatinib combination increased pCR rate



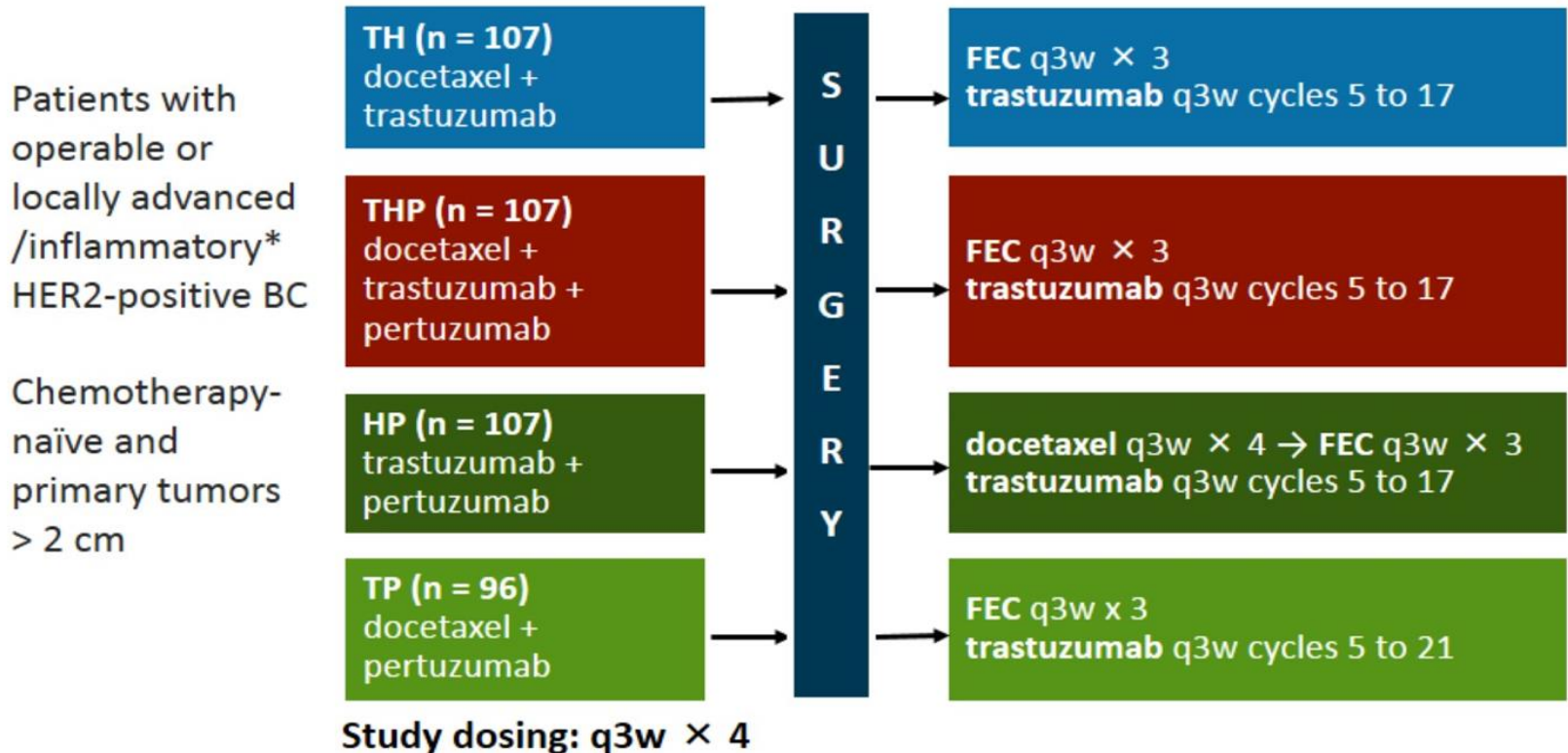
Association of clinical outcomes with pCR not with treatment arms



Role for lapatinib in HER2 positive early breast cancer

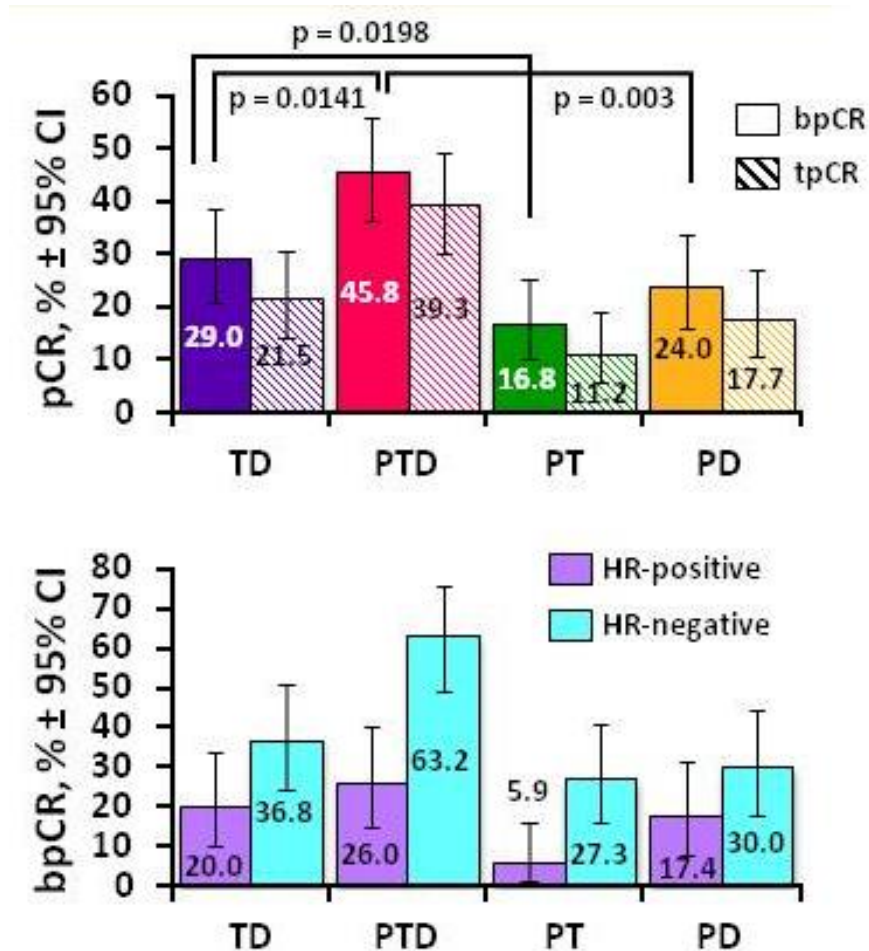
- **No DFS and OS benefit with the addition of lapatinib to trastuzumab for 1 year (ALTTO trial).**
- **No role for lapatinib in treatment of early breast cancer**
- **Higher incidence of toxicities with lapatinib**
 - ✓ **Diarrhea**
 - ✓ **Rash**
 - ✓ **Liver dysfunction**
 - ✓ **Neutropenia**
 - ✓ **Paronychia**

NeoSphere : dual HER2 blockade with pertuzumab and trastuzumab

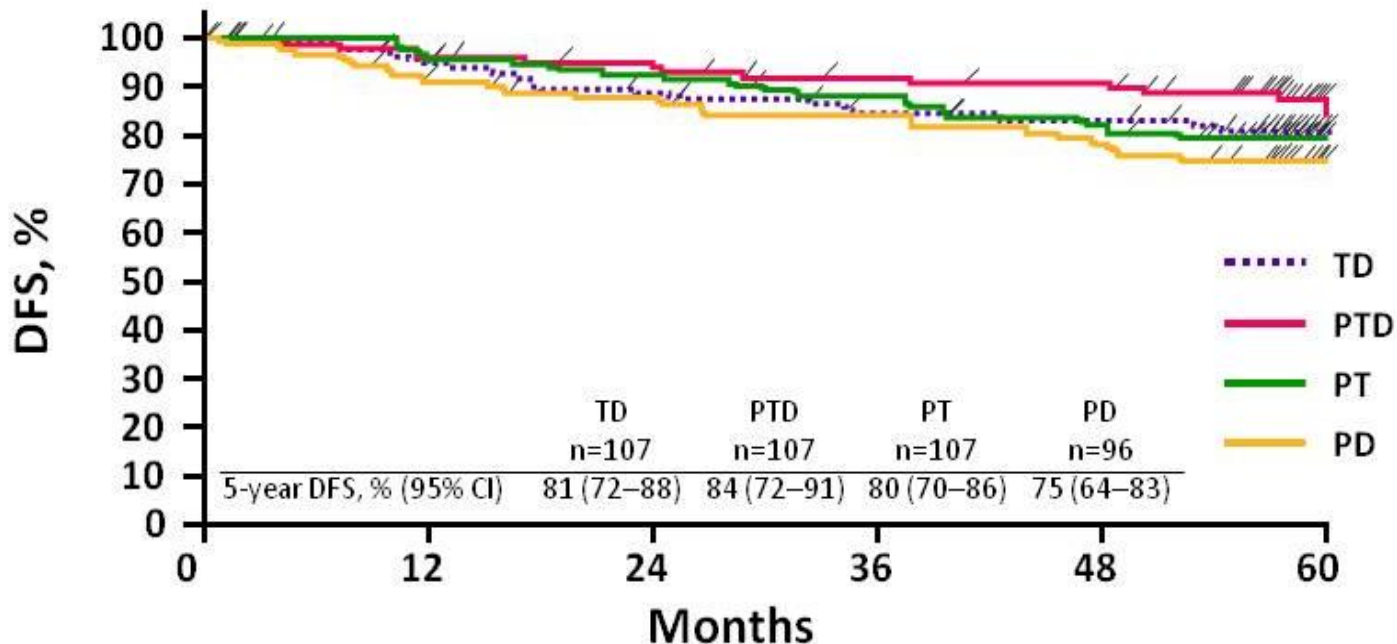


*Locally advanced = T2-3, N2-3, M0 or T4a-c, any N, M0; operable = T2-3, N0-1, M0; inflammatory = T4d, any N, M0

Higher pCR rate with dual HER2 blockade : NeoSphere trial



No difference in DFS across all four arms

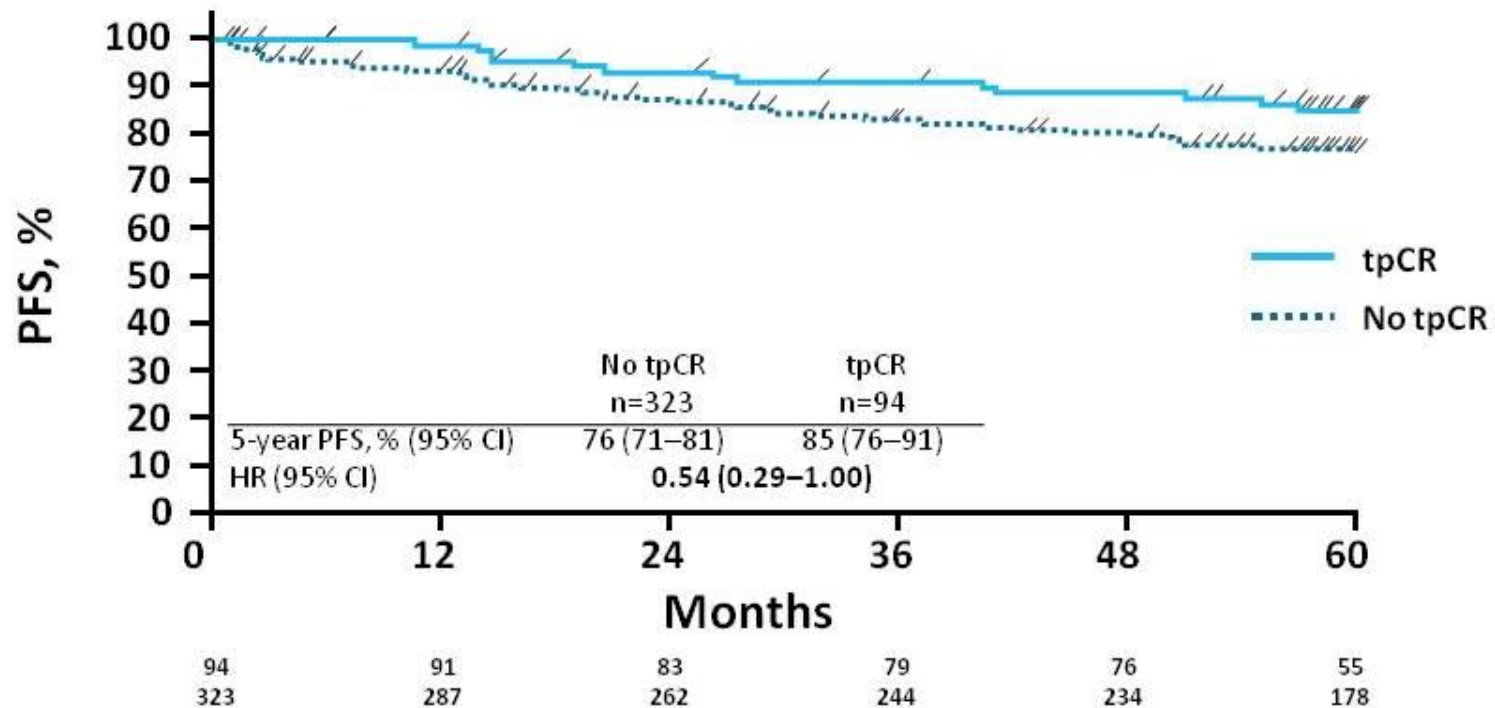


n at risk

	0	12	24	36	48	60
TD	103	92	85	79	77	12
PTD	101	96	92	88	85	17
PT	96	91	87	81	75	10
PD	92	81	76	72	66	29

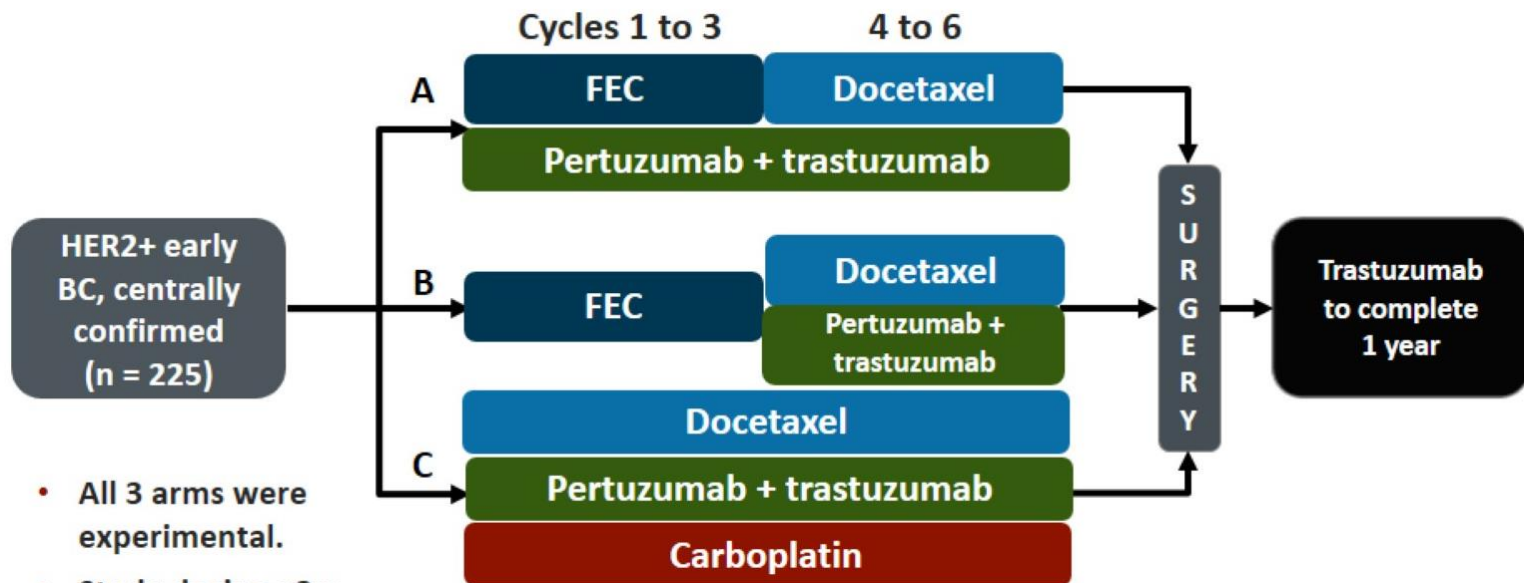
Kaplan–Meier curves are truncated at 60 months (the end of scheduled follow-up). However, summary statistics shown here take into account all follow-up. Two late events occurred with PTD: one case of PD at 67 months, and one death due to an unrelated cerebrovascular accident without PD at 72 months.

PFS by tpCR : ITT population



Kaplan–Meier curves are truncated at 60 months (the end of scheduled follow-up). However, summary statistics shown here take into account all follow-up. One late event occurred in the No tpCR group due to PD at 71 months; one late event occurred in the tpCR group, a death due to an unrelated cerebrovascular accident without PD at 76 months

TRYPHAENA : phase II neoadjuvant trastuzumab and pertuzumab in HER2+ EBC



- All 3 arms were experimental.

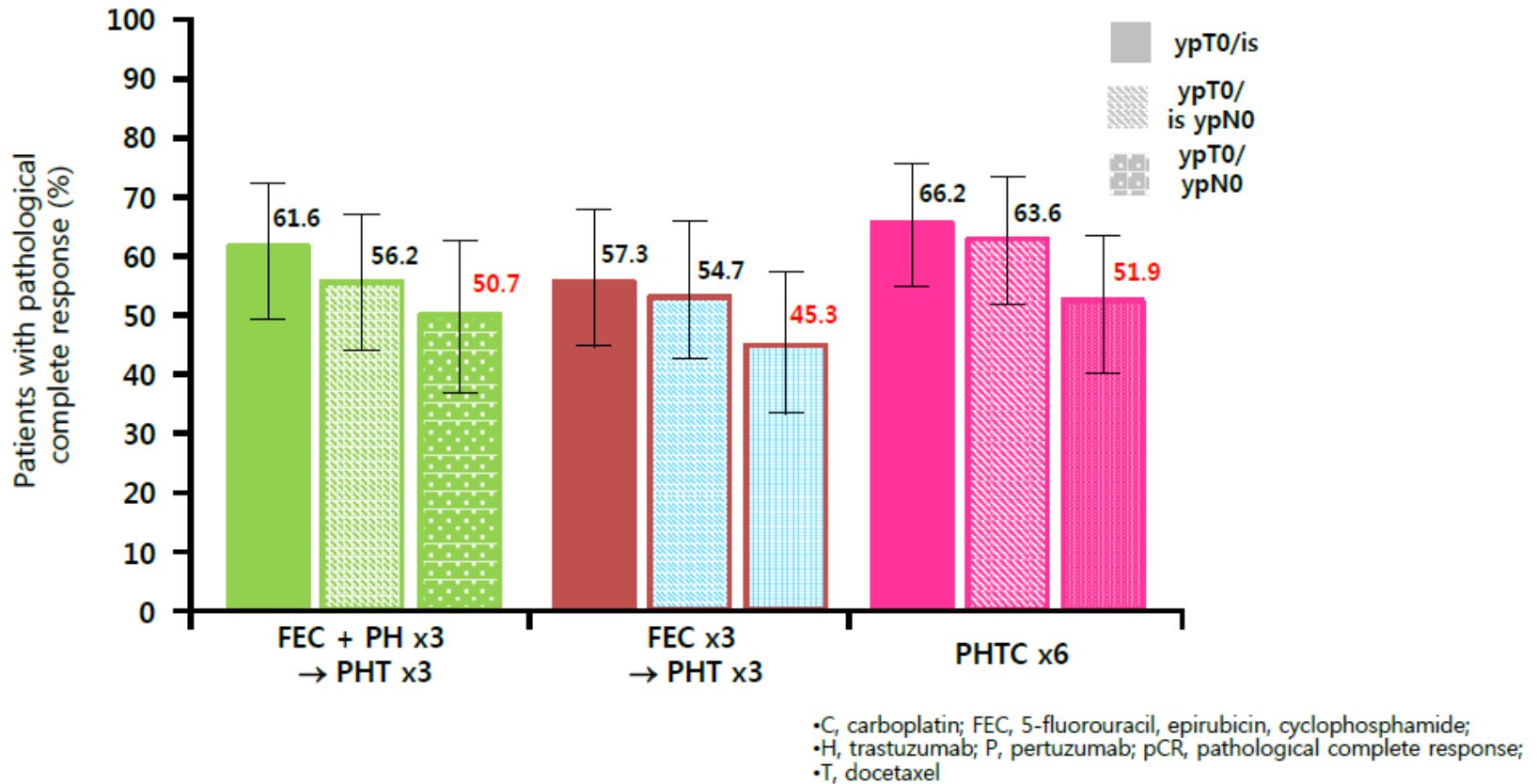
- Study dosing q3w

- FEC: 500 mg/m², 100 mg/m², 600 mg/m²
- Carboplatin: AUC 6
- Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
- Pertuzumab: 840 mg loading dose, 420 mg maintenance
- Docetaxel: 75 mg/m² (escalating to 100 mg/m² if tolerated, in arms A and B only)

- Stratification

- Operable, locally advanced, and inflammatory BC
- HR positivity

High pCR rates of regardless of chemotherapy backbone

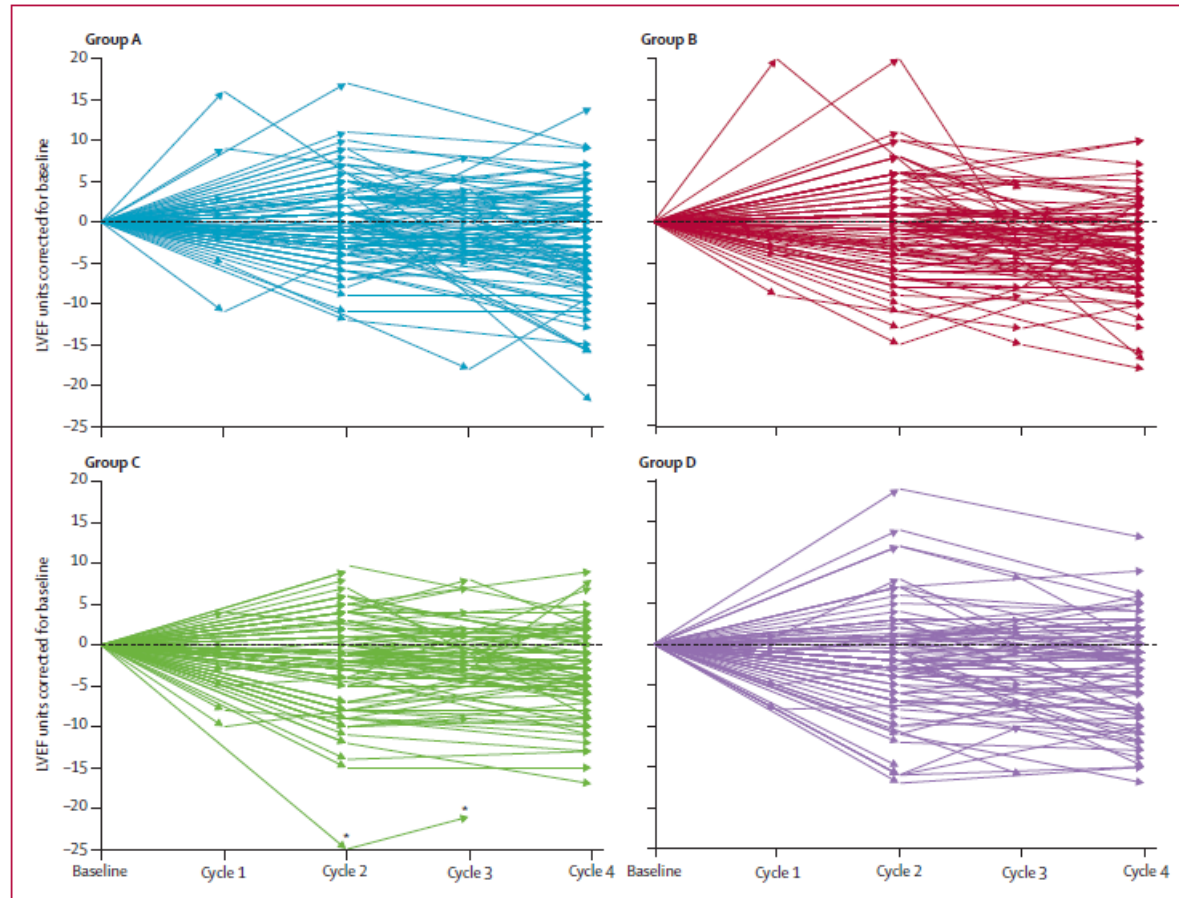
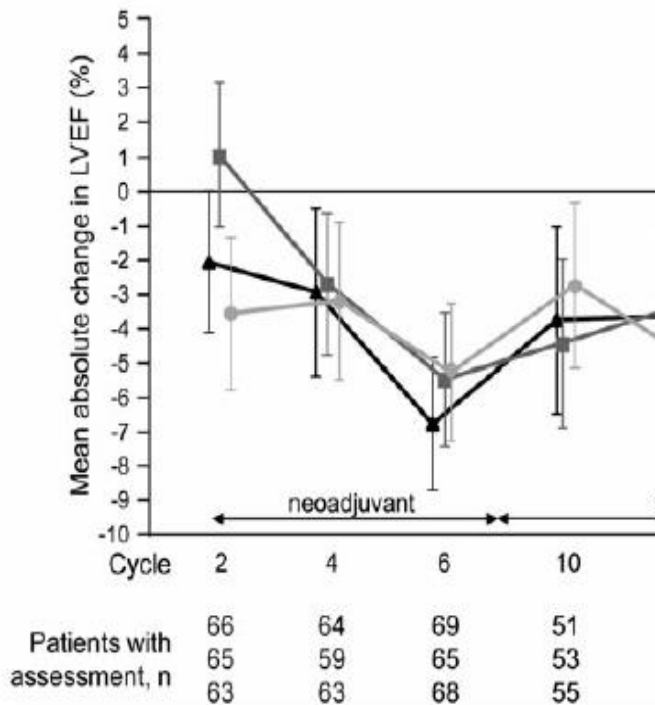


Most common adverse events of dual HER2 blockades

Lapatinib*		Pertuzumab**	
Any grade	Grade 3/4	Any grade	Grade 3/4
Diarrhea	Diarrhea	Alopecia	Febrile neutropenia
Hepatic dysfunction	Hepatic dysfunction	Neutropenia	Neutropenia
Neutropenia	Neutropenia	Diarrhea	
Rash	Rash	Nausea	
Fatigue		Fatigue	
HFS		Rash	
Mucositis		Mucositis	

*, NeoALTTO; **, NeoSphere

Cardiac safety of dual HER2 blockade : pertuzumab + trastuzumab



Should dual HER2 blockade apply to all and adjuvant setting?

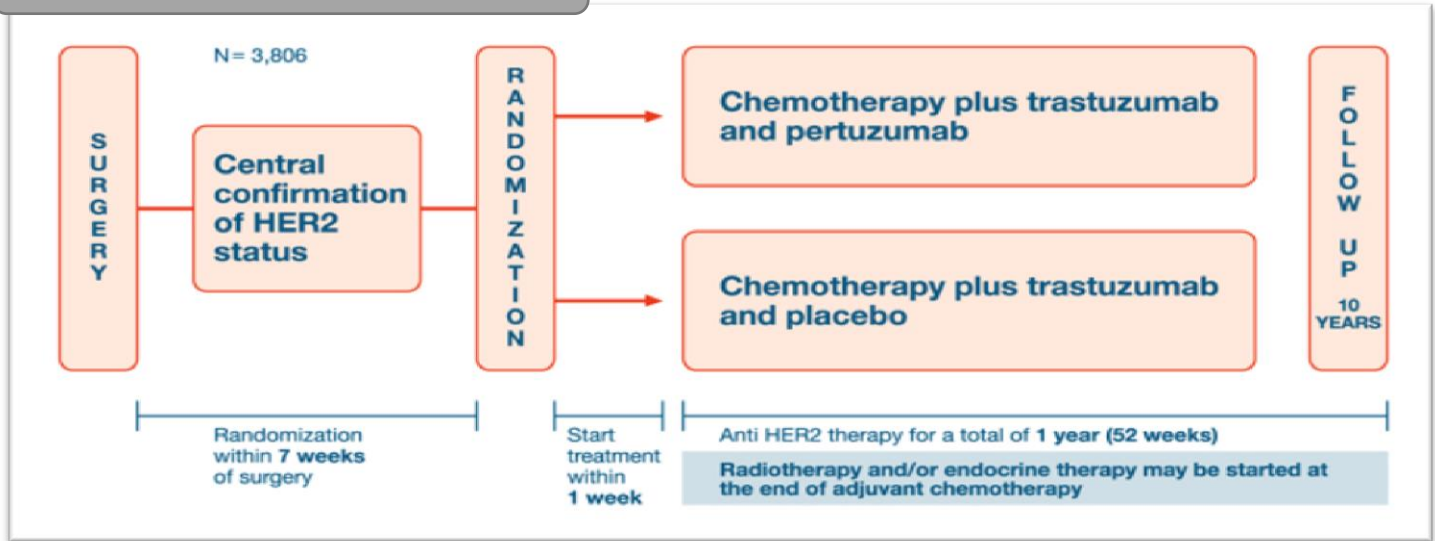
NCCN guideline 2016

Preferred regimens : (Category 2A)

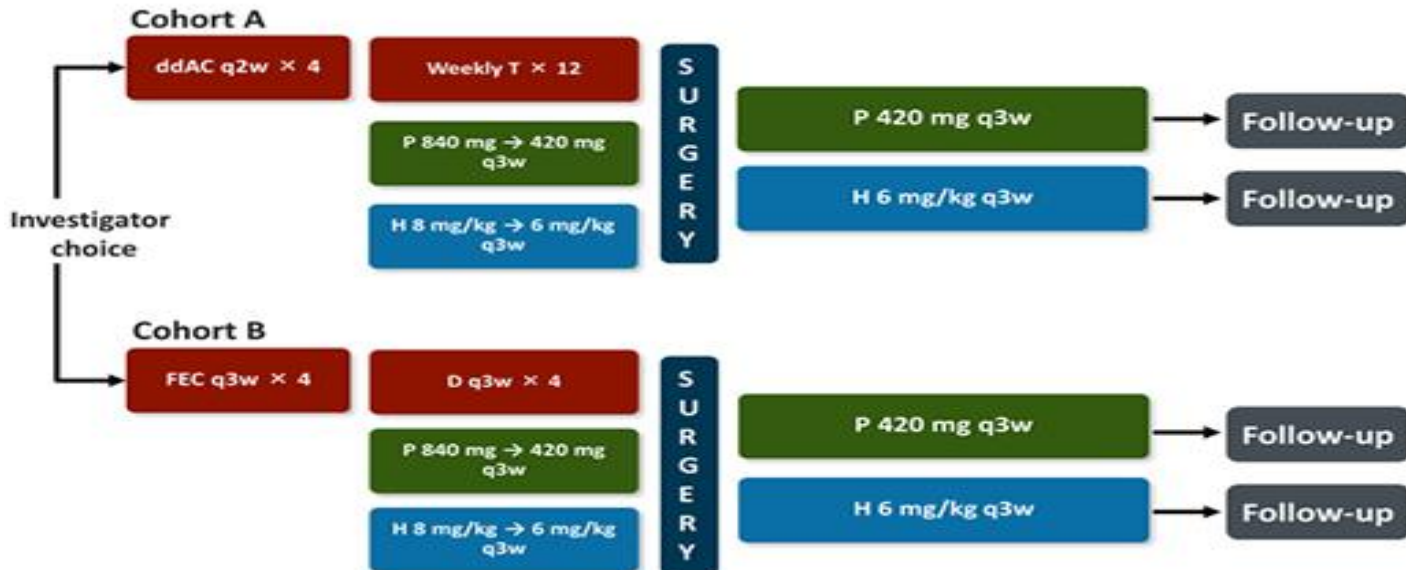
- AC → T+trastuzumab ± Pertuzumab
- TCH ± Pertuzumab

A pertuzumab containing regimen can be administered to patients with \geq T2 or \geq N1, HER2 positive EBC. **Patients who have not received a pertuzumab-containing regimen can receive adjuvant pertuzumab**

APHINITY trial



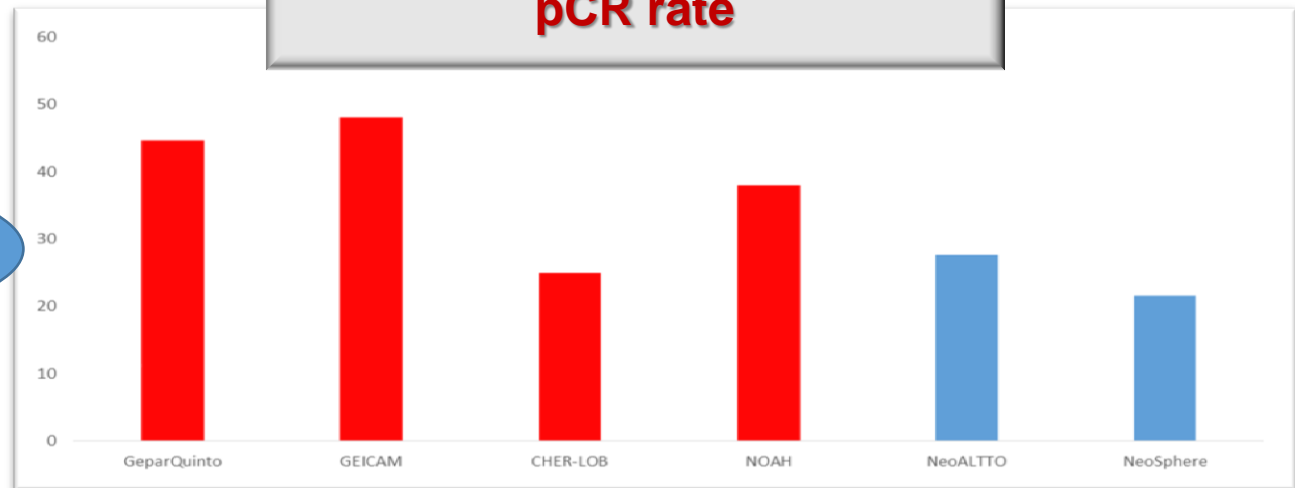
BERENICE trial



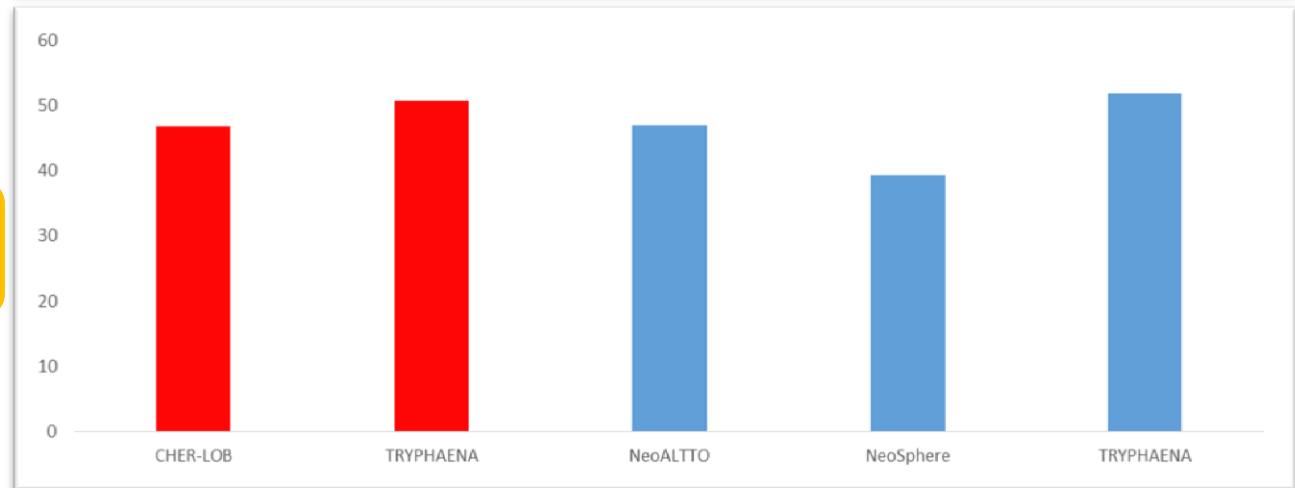
Is it necessary to include anthracycline?

pCR rate

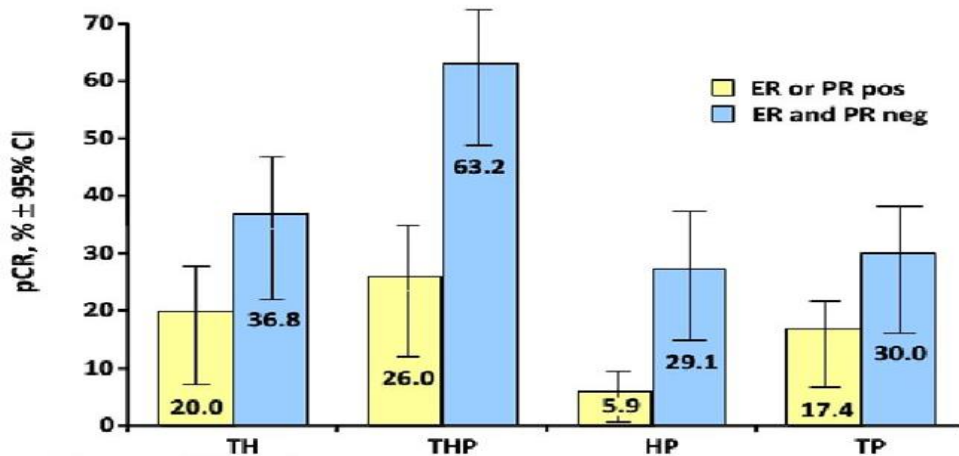
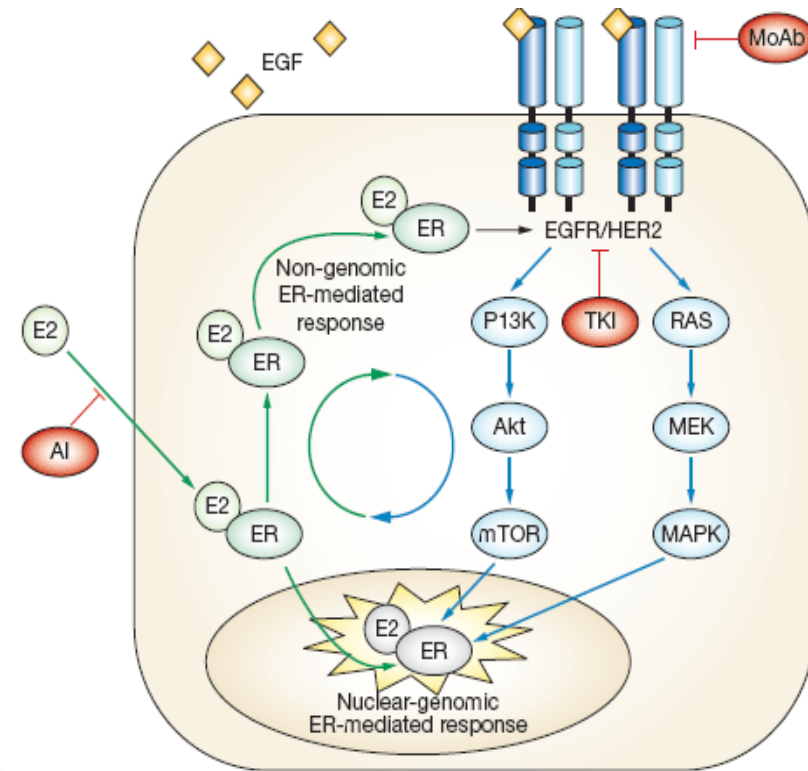
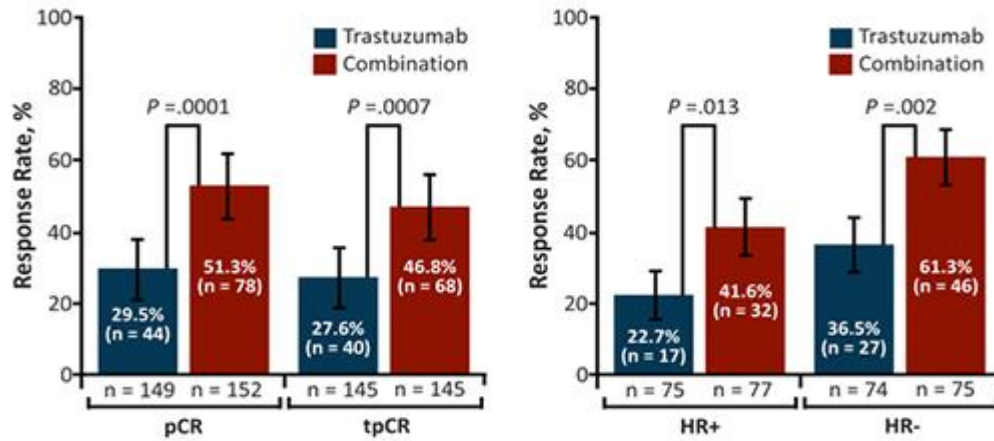
Trastuzumab
only



Combination



Lower efficiency in HR+/HER2+ EBC



uzumab; P, pertuzumab; T, docetaxel

Ongoing clinical trials with anti-HER2 therapy in neoadjuvant setting

- T-DM1 (Ado-trastuzumab emtansine) plus pertuzumab (**Kristine trial**)
- Trastuzumab + BKM120 (oral pan-class I PI3K inhibitor)
(**NeoPHOEBE**)
- **Neratinib** and/or trastuzumab + paclitaxel
- THP (docetaxel + trastuzumab + pertuzumab) ± **Fulvestrant** in HR+/HER2+ EBC
- T-DM1 vs. Trastuzumab as adjuvant therapy after preop therapy
(**KATHERINE**)