Neoadjuvant therapy for HER2-overexpressing and triple negative breast cancers

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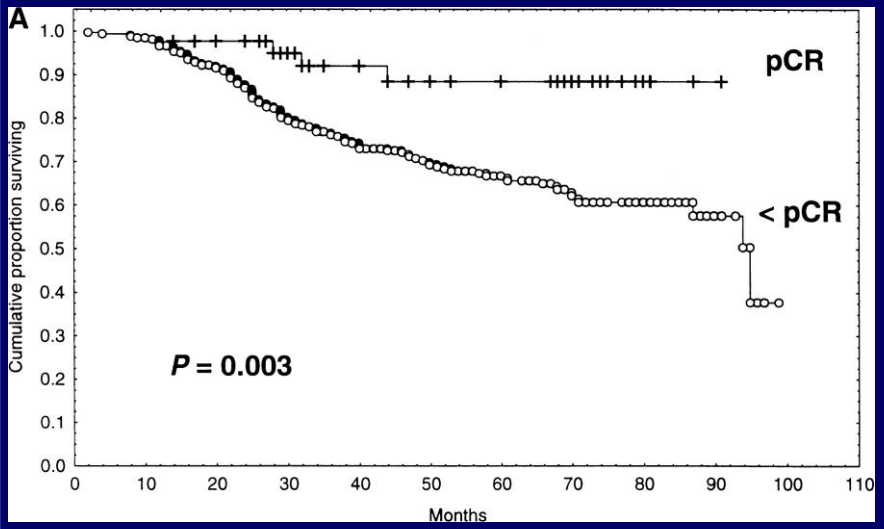
learning to care

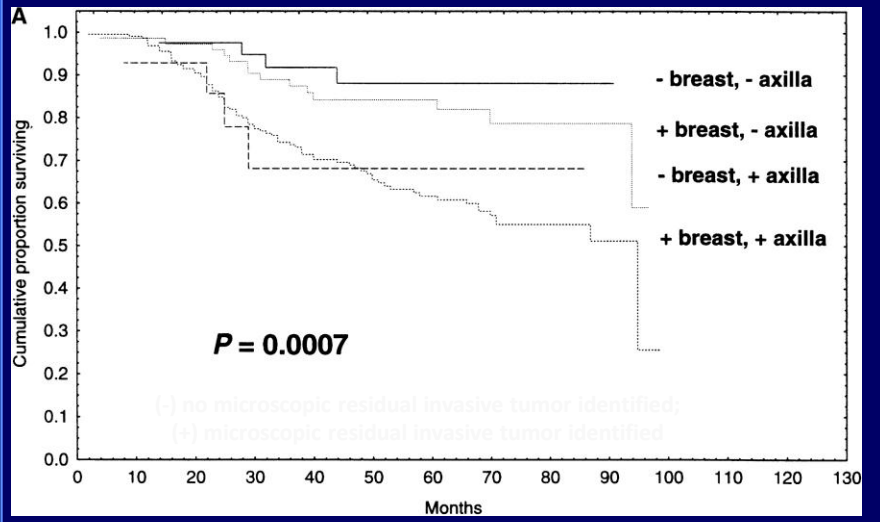
OS RATES IN RELATION TO pCR RATES

MD Anderson experience (Kuerer et al, JCO 1999)

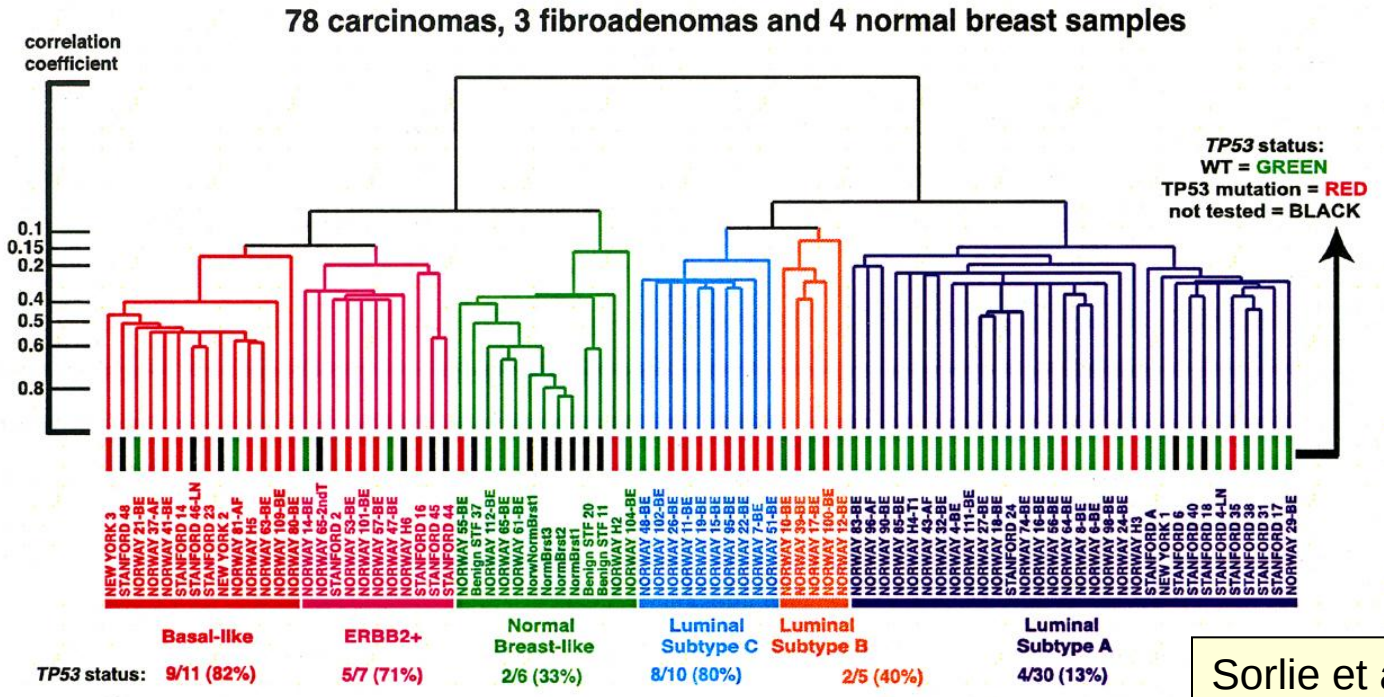
- 272 LABC pts treated by anthracycline-based NAC
- pCR= 12%



Relationship between OS and pCR in primary tumor and axillary lymph nodes



Relationship between OS and differential pCR irates in breast and axilla



Sorlie et al *PNAS* 2001

pCR% depends on cellular type
and on **molecular type**

N=22
10 pCR (45%)
61 genes signature

N=20
9 pCR (45%)
no signature identified

N=28
2 pCR

Rouzier et al. Clin Cancer Res 2005

I-SPY: Neoadjuvant Chemotherapy for Breast Cancer and Biomarker Analysis

I-SPY: study to identify biomarkers of response to neoadjuvant CT

	ER (*P* < .0001)		PgR (*P* < .0001)		HER2 (*P* = .02)		Ki67 Index (*P* < .0001)		
	+ (n = 115)	– (n = 88)	+ (n = 95)	– (n = 107)	+ (n = 28)	– (n = 137)	Low (n = 50)	Int (n = 62)	High (n = 70)
pCR^{+}	16%	44%	12%	43%	39%	18%	10%	16%	43%

- Tumor **basal** (ER^{-}/PgR^{-}/HER2^{-}), **luminal B** (ER^{+}/PgR^{+}/HER2^{+}), and **HER2** (ER^{-}/PgR^{-}/HER2^{+}) associated with **higher pCR rates**
- **Luminal A** (ER^{+}/PgR^{+}/HER2^{-}) showed **low pCR (9%)**
- **ER^{-}/HER2^{+}** tumors showed **higher pCR (88%)** compared to ER^{+}/HER2^{+} tumors (25%)

PER PHYSICIANS' EDUCATION RESOURCE

Livasy et al. SABCS 2008. Abstract 5102.

Neoadjuvant therapy for HER-2+ breast cancer

- **The role of neoadjuvant trastuzumab**
- **Anti-HER-2 agent in neoadjuvant or adjuvant setting?**
- **Other anti-HER-2 agents**
- **Dual blockade**
- **Which chemotherapy?**
- **Biomarkers**

Meta-analysis: Neoadjuvant anthracyclines/taxanes with or without trastuzumab

All cooperative neoadjuvant trials in Germany between 1998 and 2006 using anthra/taxanes (N=4913) plus GeparQuattro and TECHNO trials (N=1721) using trastuzumab for HER2+ tumors

Goals:

Total 6634 pts

- Overall pCR rate
- Effects according to treatment:
  - Trastuzumab
  - Dose-Density
  - Duration
  - Concurrent versus sequential

PER PHYSICIANS' EDUCATION RESOURCE

Von Minckwitz et al, SABCS 2008, Abstract 79

Meta-analysis: pCR rate based on treatment

In patients with HER2+ tumors:

	Trastuzumab (N=671)	No Trastuzumab (N=736)	P-value
pCR rate	**41%**	**23%**	<.001

Other characteristics associated with high rate of pCR (multivariate analysis):

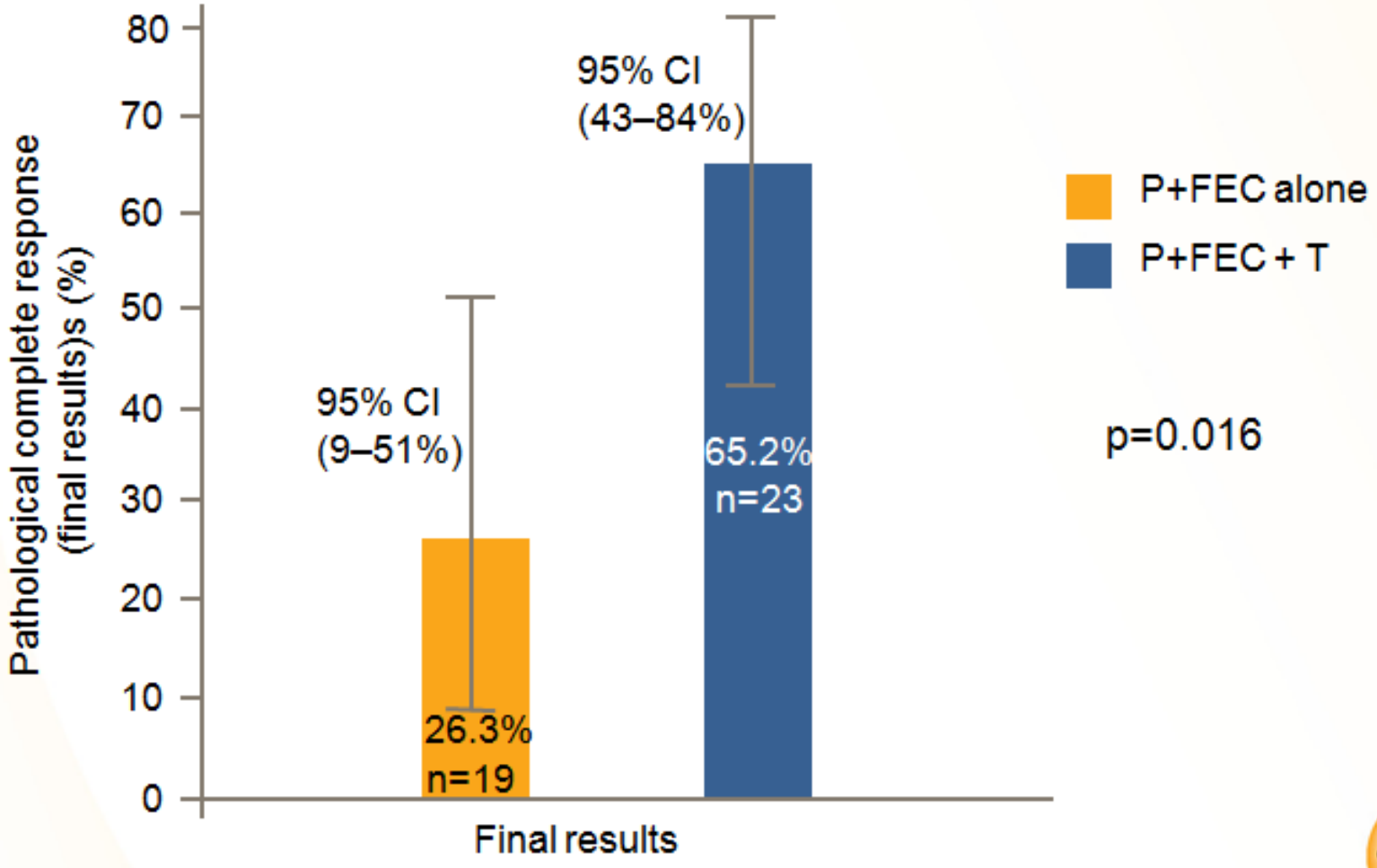
Younger age (P<.001)
Ductal (P<.001)
Histological grade 3 (p<.001)
Positive HER2 (P<.001)
Negative HR (P<.001)
Tumor size (P<.001)
Conventional dosage (vs. dd) (P<.001)

No significant difference between concurrent vs. sequential therapy (P=.329)

PER PHYSICIANS' EDUCATION RESOURCE

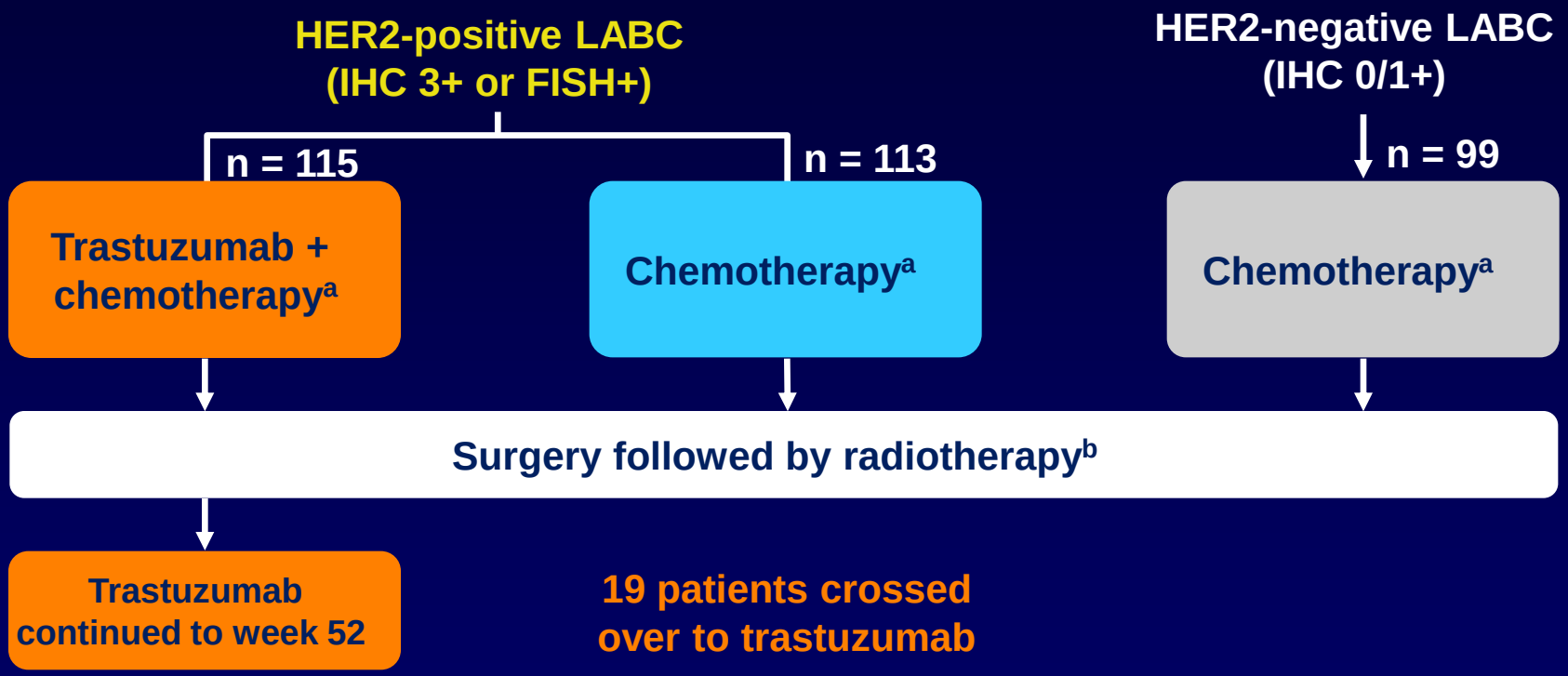
Von Minckwitz, SABCS 2008, Abstract 79

MD Anderson Neoadjuvant Trastuzumab randomised study: pathological complete response rate



P, paclitaxel; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; T, trastuzumab
Buzdar *et al. J Clin Oncol* 2005;23:3676–85

NOAH: Phase III, Open-Label Trial of Neoadjuvant Trastuzumab

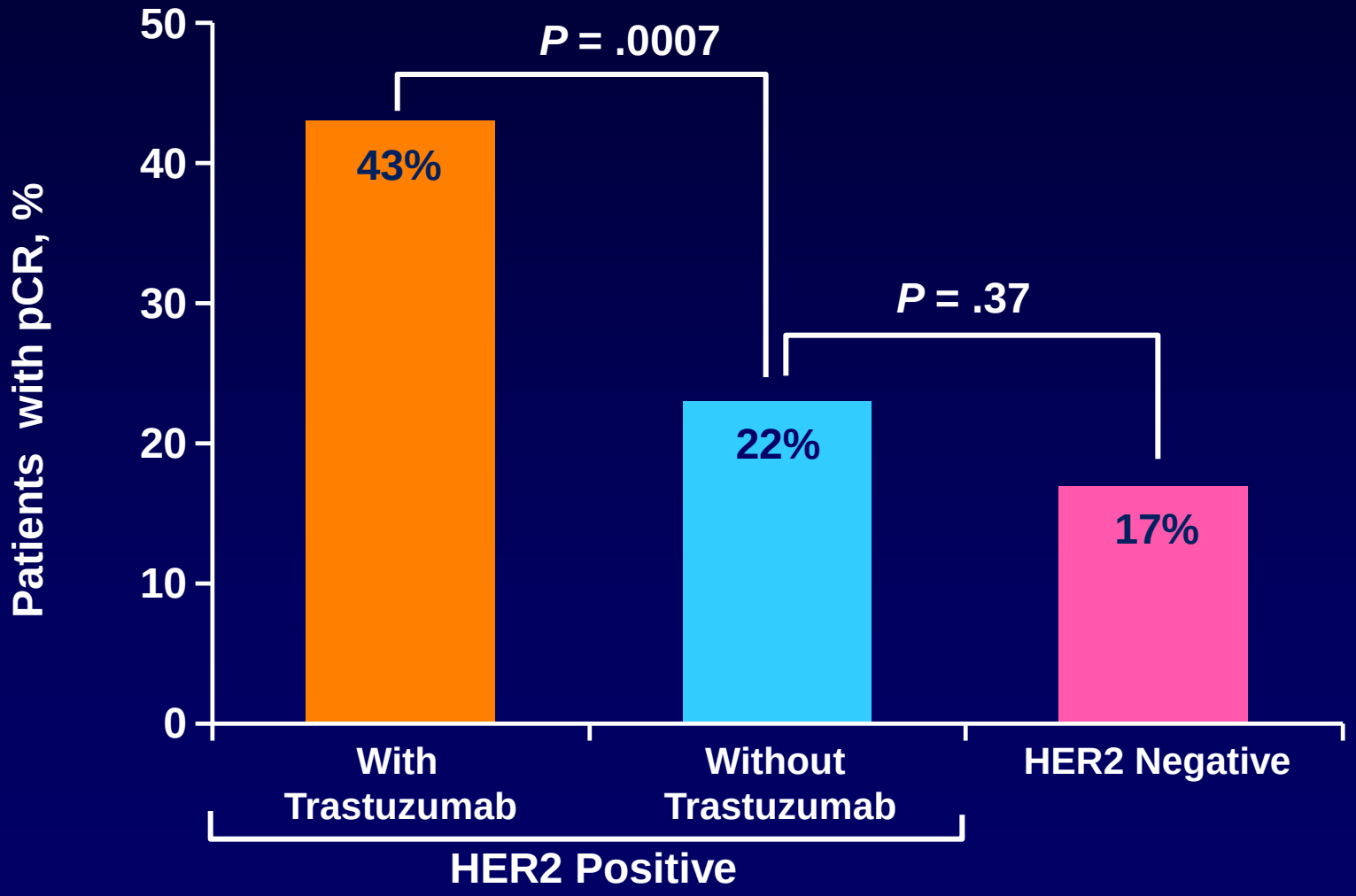


[a] CT: AP x 3 followed by P x 4, followed by CMF x 3

[b] HR+ pts received adjuvant tamoxifen

Gianni L, et al. *Lancet.* 2010;375(9712):377-384.

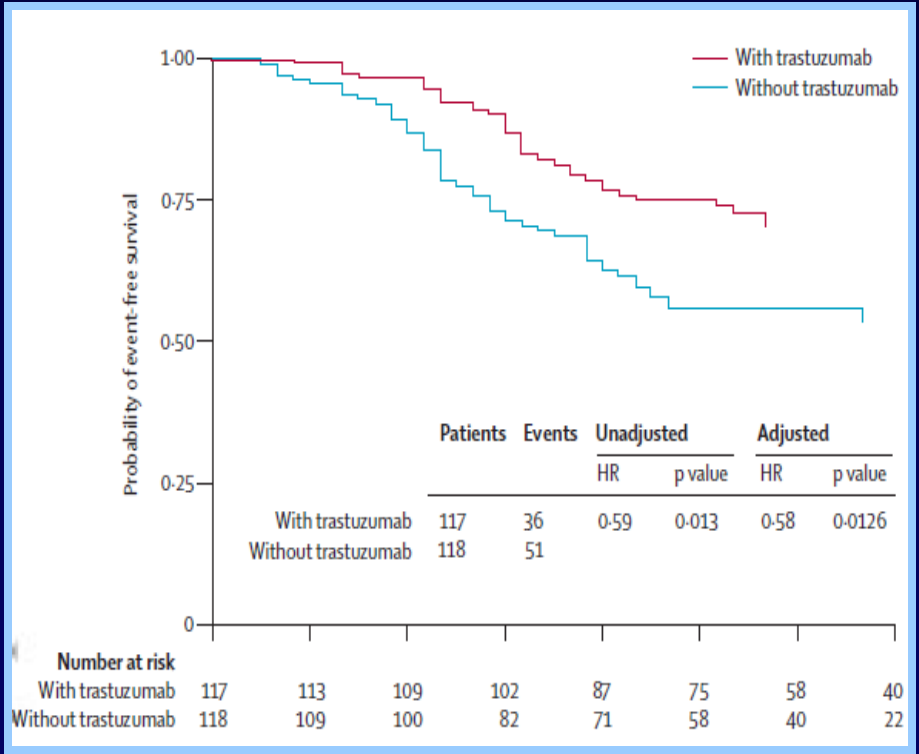
NOAH Trial: Trastuzumab Improves pCR Rates in HER2-Positive LABC



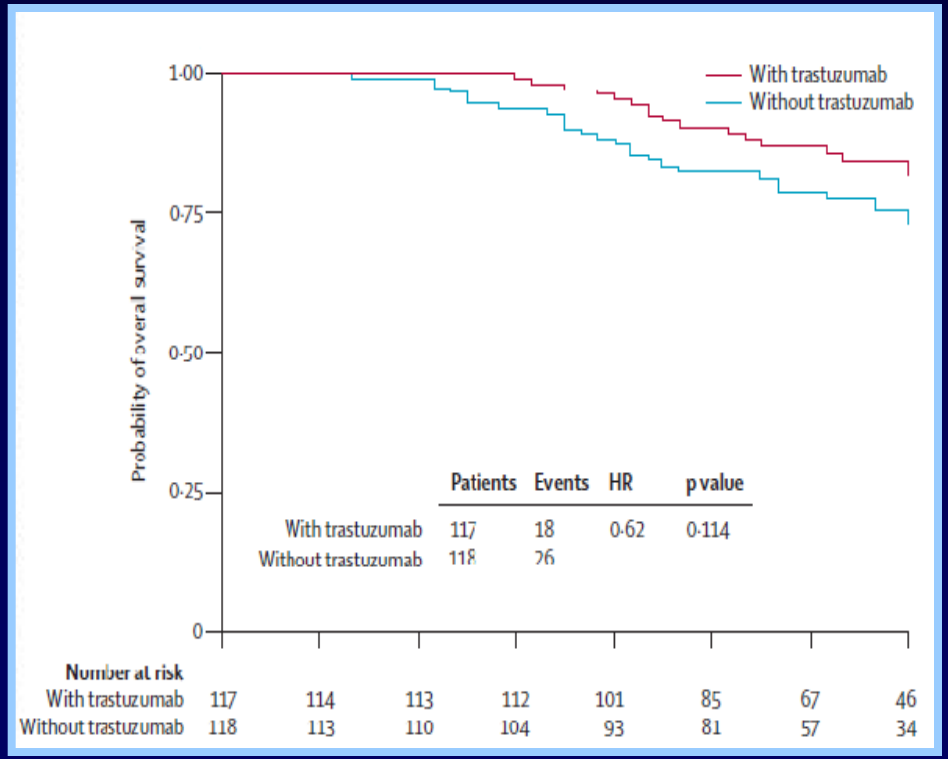
Gianni L, et al. *Lancet.* 2010;375(9712):377-384.

NOAH: Event-Free Survival (EFS) and OS in HER2-Positive Population (ITT)

EFS

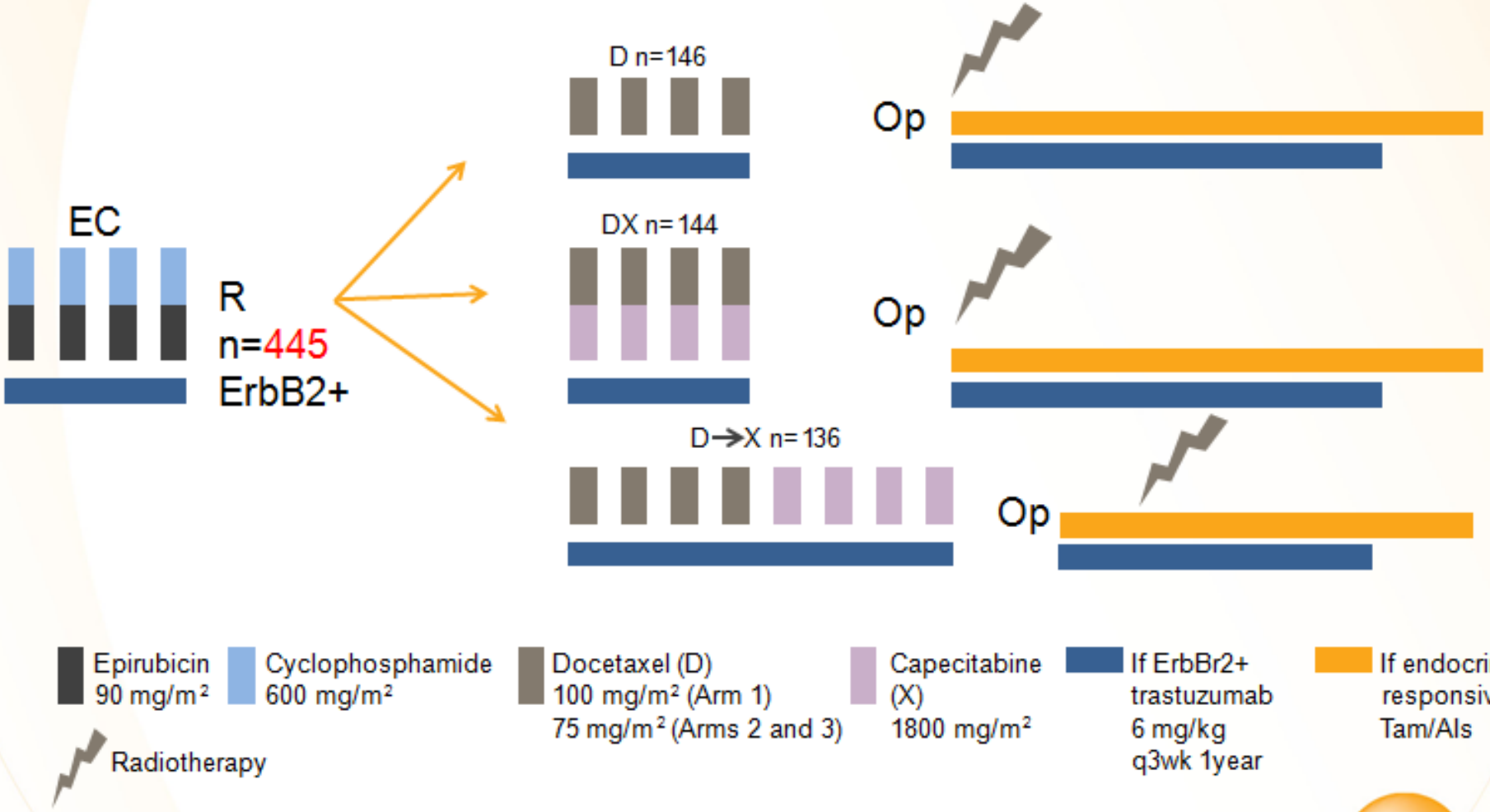


OS



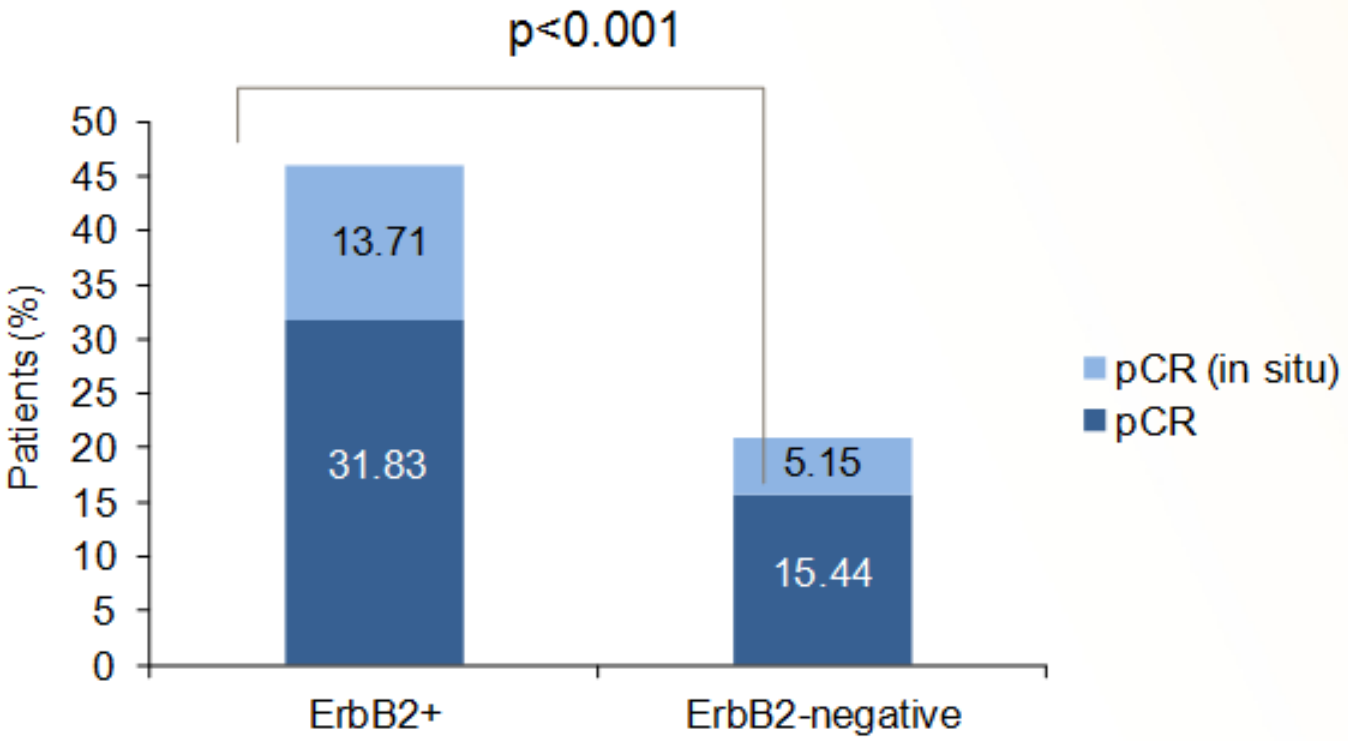
Gianni L, et al. *Lancet.* 2010;375(9712):377-384.

GeparQuattro study design



AI, aromatase inhibitor; C, cyclophosphamide; E, epirubicin; D, docetaxel; Op, surgery; R, randomisation; Tam, tamoxifen; X, capecitabine

GeparQuattro study results: pathological complete response



When trastuzumab was added in patients with HER-2+ disease (n=445), the pCR rate rose significantly to 31.8% (p<0.001).

pCR, pathological complete response. Defined as grades 4 and 5 on a modified regression scale (grade 5, no microscopic evidence of residual viable tumour cells (invasive or non-invasive) in breast and nodes; grade 4, no residual tumour in breast tissue, but involved nodes)

Untch *et al. J Clin Oncol* 2010;28:2024–31

oncology academy

Neoadjuvant therapy for HER-2+ breast cancer

- **Anti-HER-2 agent in neoadjuvant or adjuvant setting?**

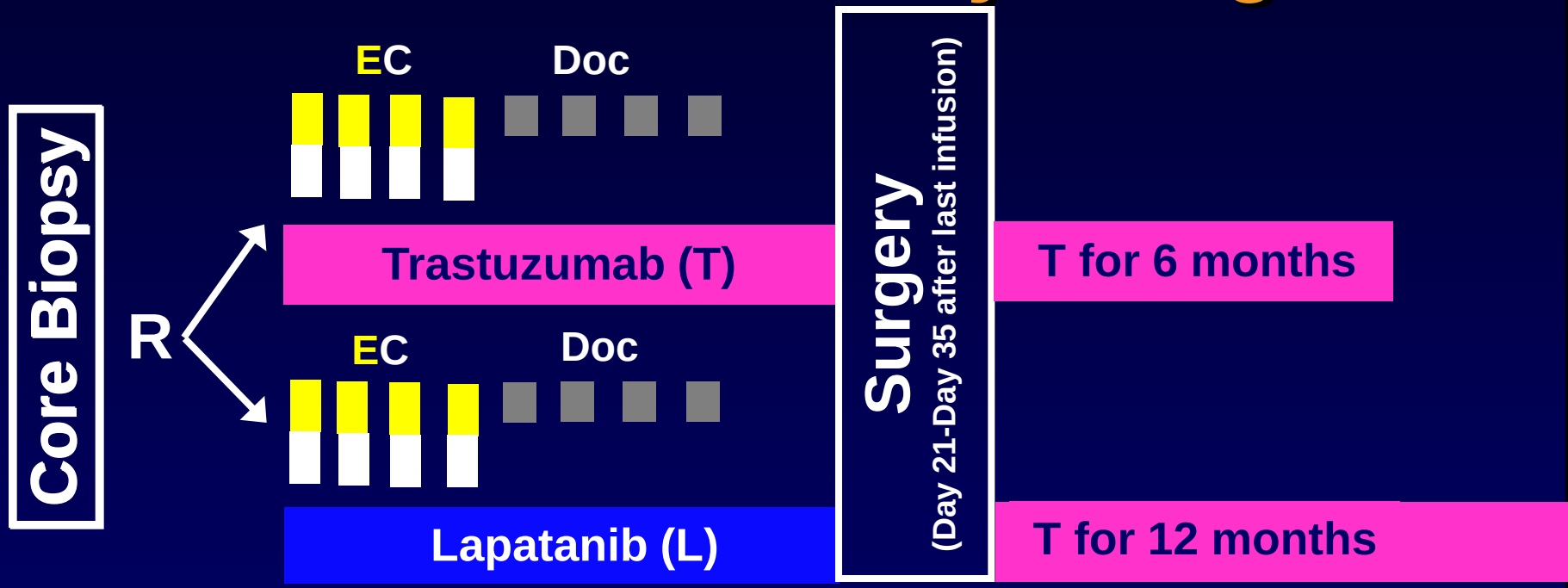
NO DIRECT COMPARISON ADJUVANT VS. NEOADJUVANT

INDIRECT EVIDENCE (Higher pCR rates!!)

Neoadjuvant therapy for HER-2+ breast cancer

- The role of neoadjuvant trastuzumab
- Anti-HER-2 agent in neoadjuvant or adjuvant setting?
- **Other anti-HER-2 agents**
- Dual blockade
- Which chemotherapy?
- Biomarkers

GeparQUINTO HER2-Positive Study Design



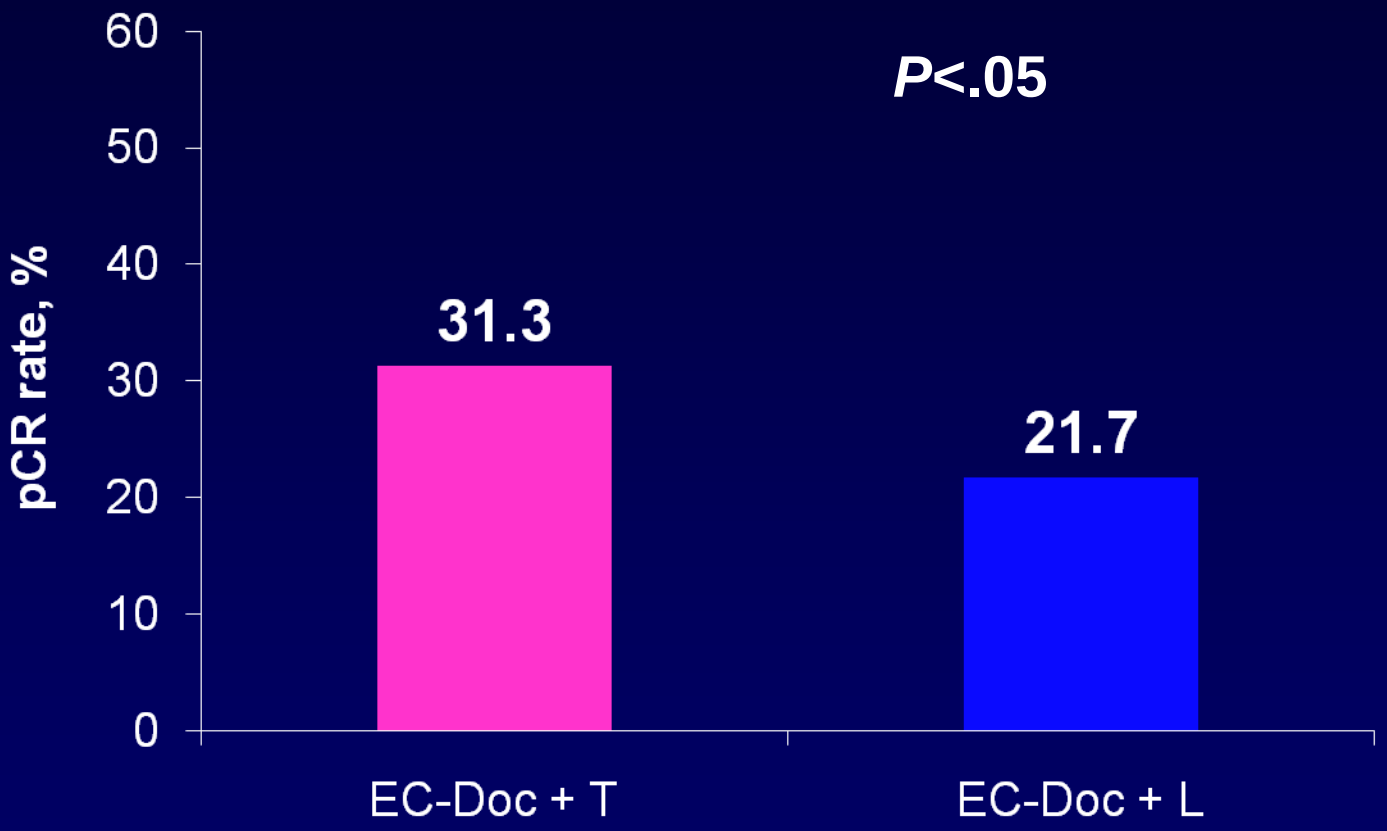
E: Epirubicin 90 mg/m^2
C: Cyclophosphamide 600 mg/m^2
Doc: Docetaxel 100 mg/m^{2*} + G-CSF

T: Trastuzumab 6 (8) mg/kg
L: Lapatinib 1250-1000 mg/day orally (all 3-week cycles)

G-CSF = granulocyte colony-stimulating factor; R = randomized

Untch M, et al. *Cancer Res.* 2010;70(24 Suppl): Abstract S3-1.

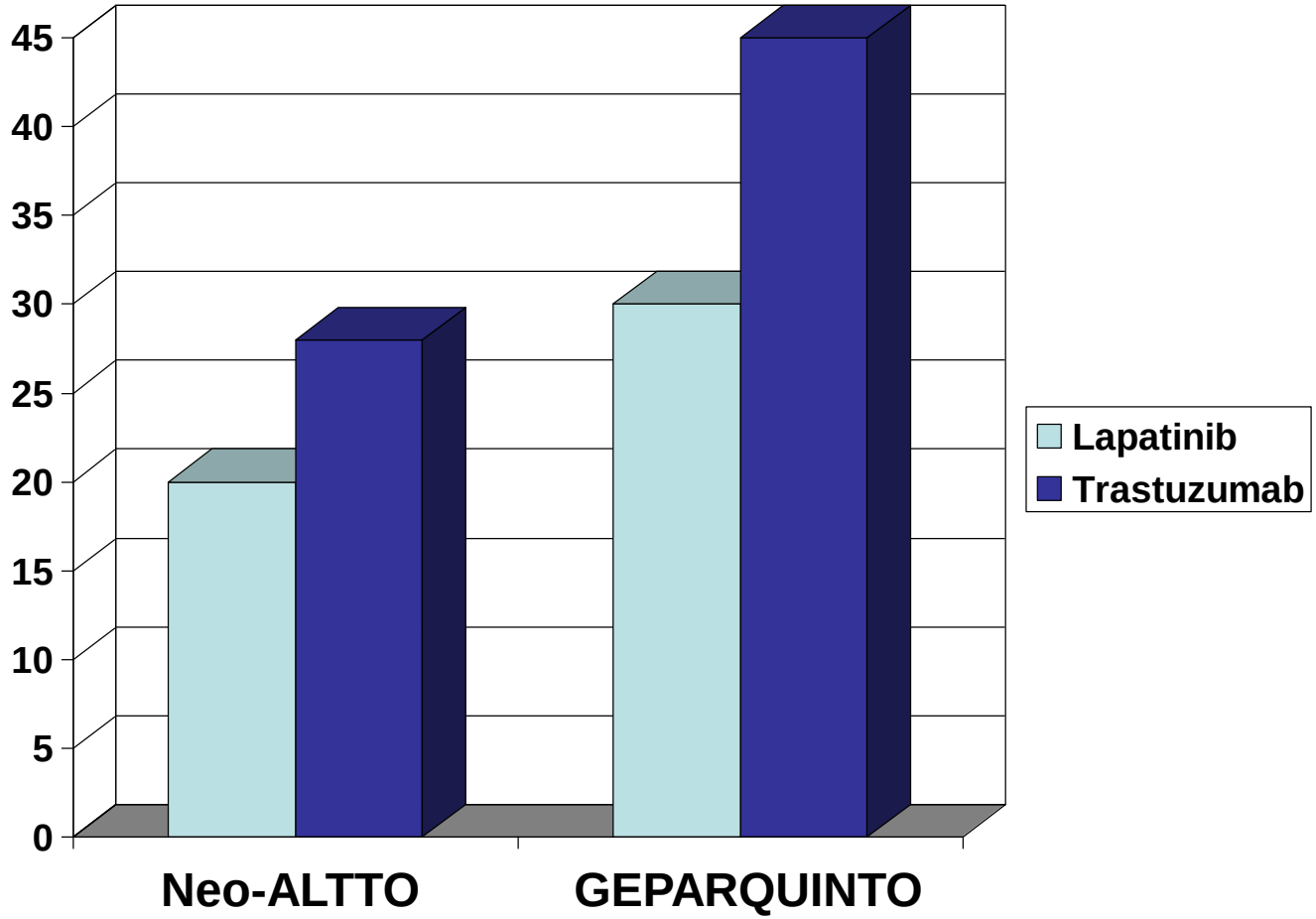
Pathologic Complete Response



Doc = docetaxel; EC = epirubicin + cyclophosphamide; L = lapatinib; pCR = pathologic complete response; T= trastuzumab

Untch M, et al. *Cancer Res.* 2010;70(24 Suppl): Abstract S3-1.

Pathologic Complete Response Trastuzumab/Chemo vs Lapatinib/ Chemo



Inability to give planned doses of lapatinib ~35% in both studies

Courtesy E. Winer

Neoadjuvant therapy for HER-2+ breast cancer

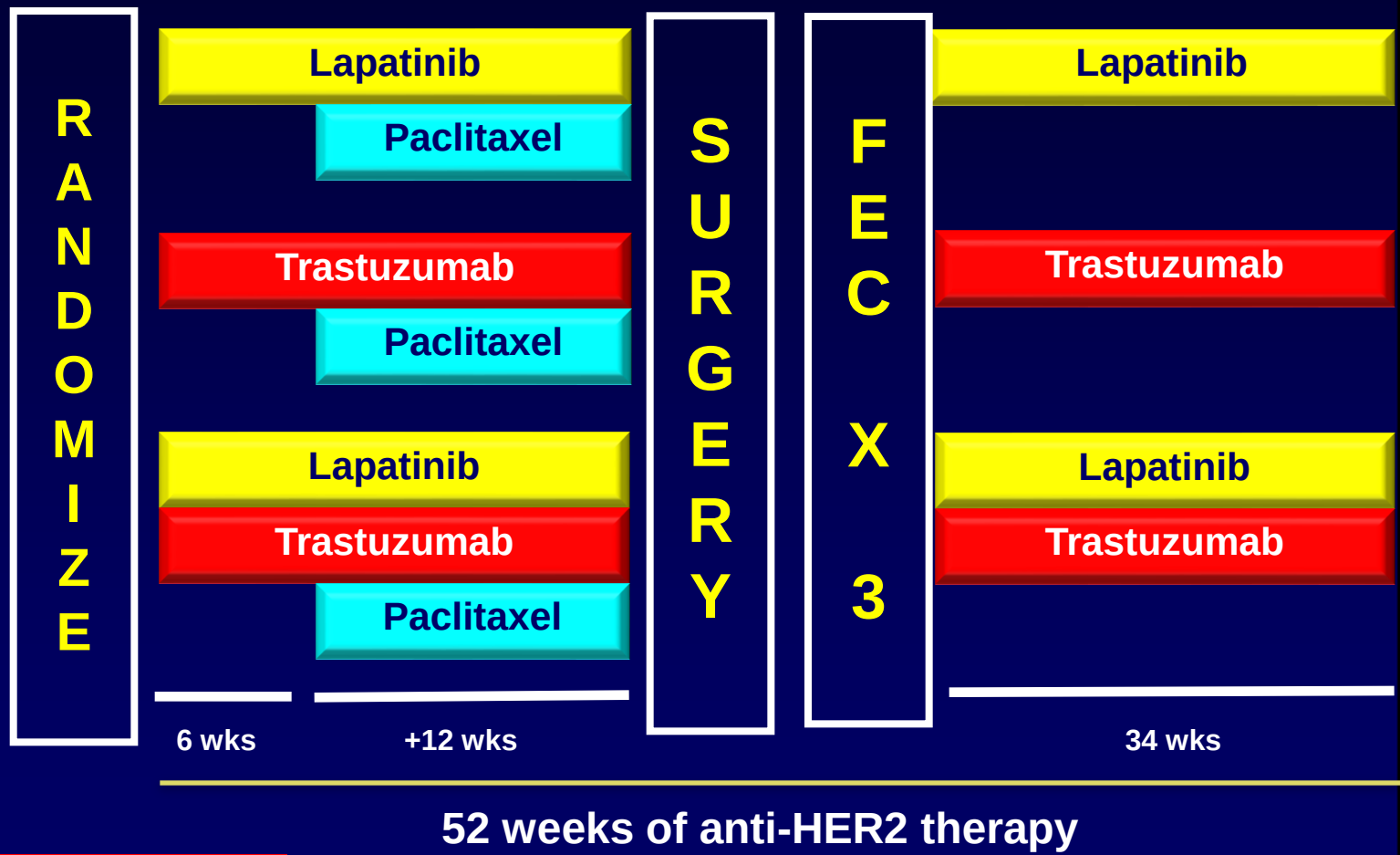
- The role of neoadjuvant trastuzumab
- Anti-HER-2 agent in neoadjuvant or adjuvant setting?
- Other anti-HER-2 agents
- **Dual blockade**
- Which chemotherapy?
- Biomarkers

NeoALTTO Study Design

- Invasive operable HER2+ BC
- T >2 cm (inflammatory BC excluded)
- LVEF ≥50%

N = 450

Stratification
- T≤5 cm vs T>5 cm
- ER or PgR+ vs ER & PgR-
- N0-1 vs N≥2
- Conservative surgery or not

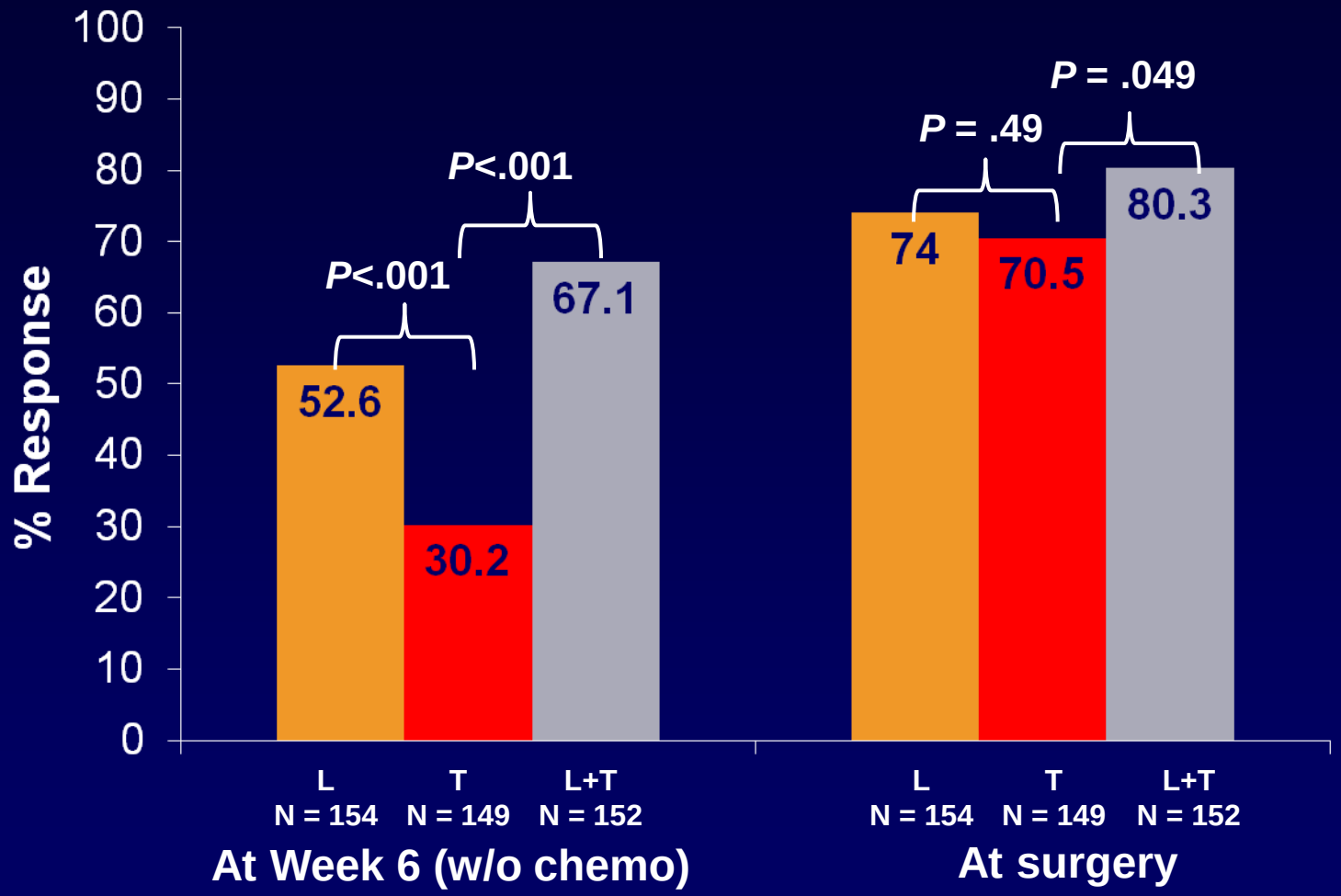


IBC exclusion criteria

Baselga J, et al. *Cancer Res.* 2010;70(24 Suppl): Abstract S3-3.

NeoALTTO: Overall Clinical Response

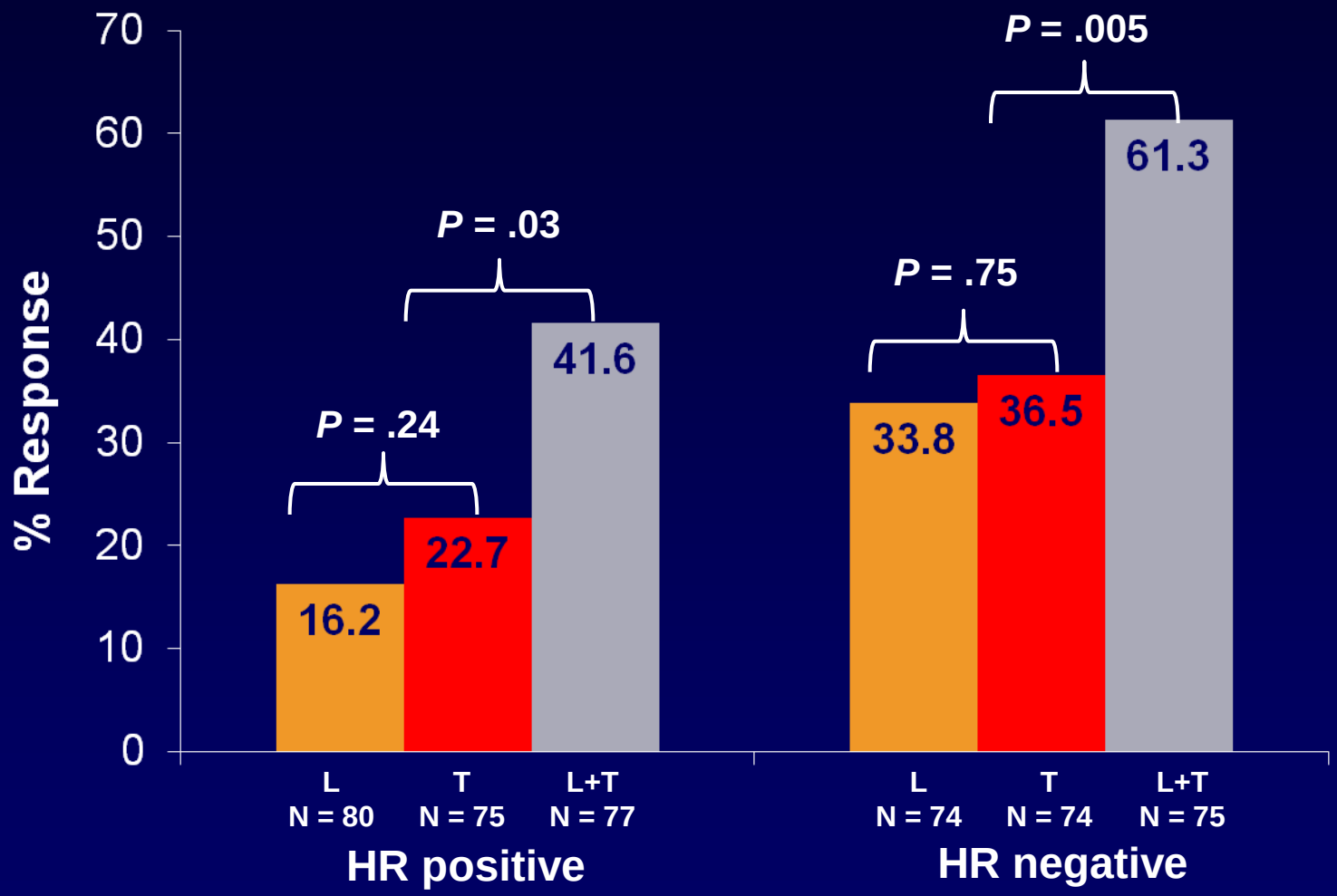
at 6 weeks (w/o chemo) and at surgery



L = lapatinib; T = trastuzumab

Baselga J, et al. *Cancer Res.* 2010;70(24 Suppl): Abstract S3-3.

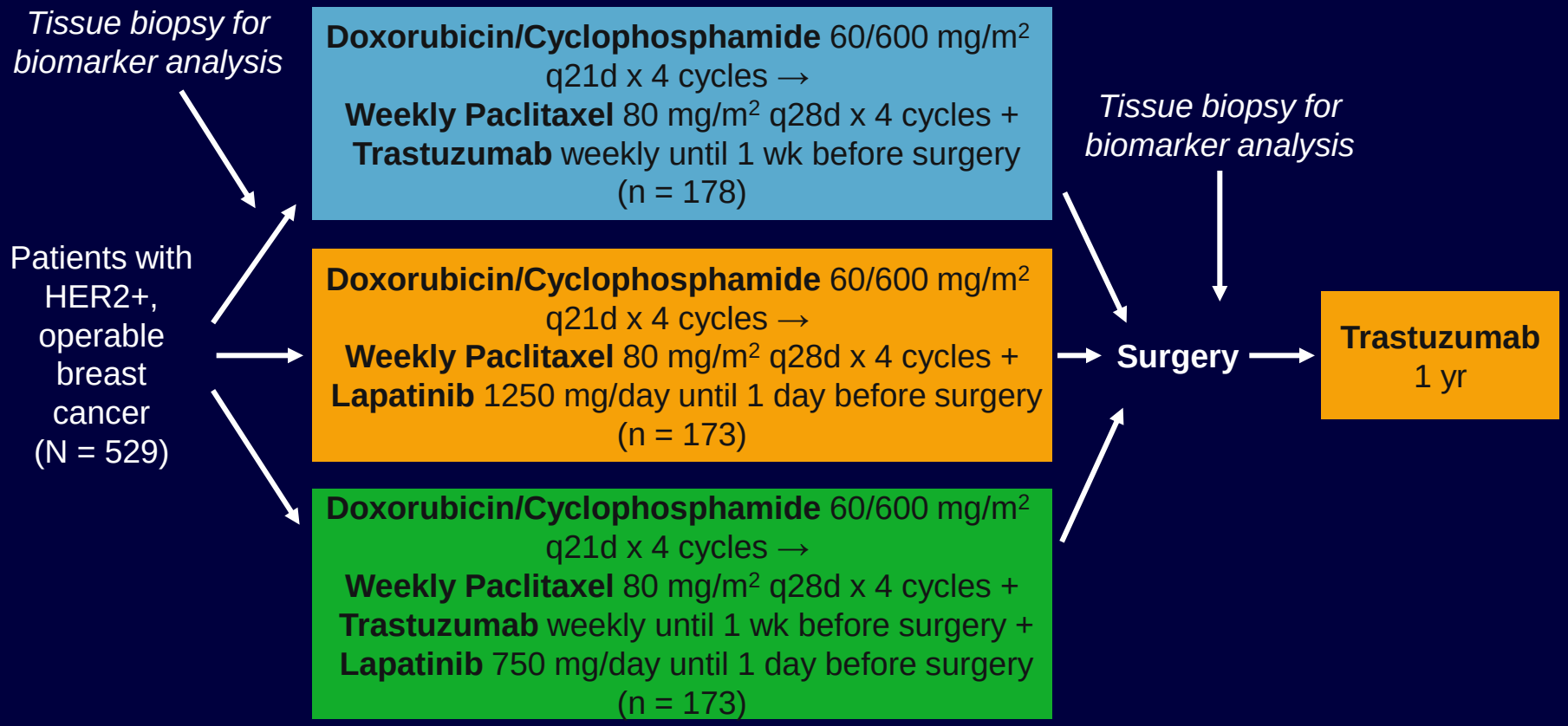
NeoALTTO: pCR by HR Status



HR = hormone receptor; L = lapatinib; pCR = pathologic complete response; T = trastuzumab

Baselga J, et al. *Cancer Res.* 2010;70(24 Suppl): Abstract S3-3.

NSABP B-41: Lapatinib in Neoadjuvant Treatment of HER2+ Breast Cancer



- Primary endpoint: pCR
- Secondary endpoints: pCR in N0, toxicity, cCR, RFS, OS

Robidoux A, et al. ASCO 2012. Abstract LBA506.

Lapatinib in Neoadjuvant Treatment of HER2+ Breast Cancer (NSABP B-41): pCR

Regimen	n	pCR*, %	*P* Value†
AC → WP + T	176	49.4	
AC → WP + L	171	47.4	.78
AC → WP + T + L	171	60.2	.056

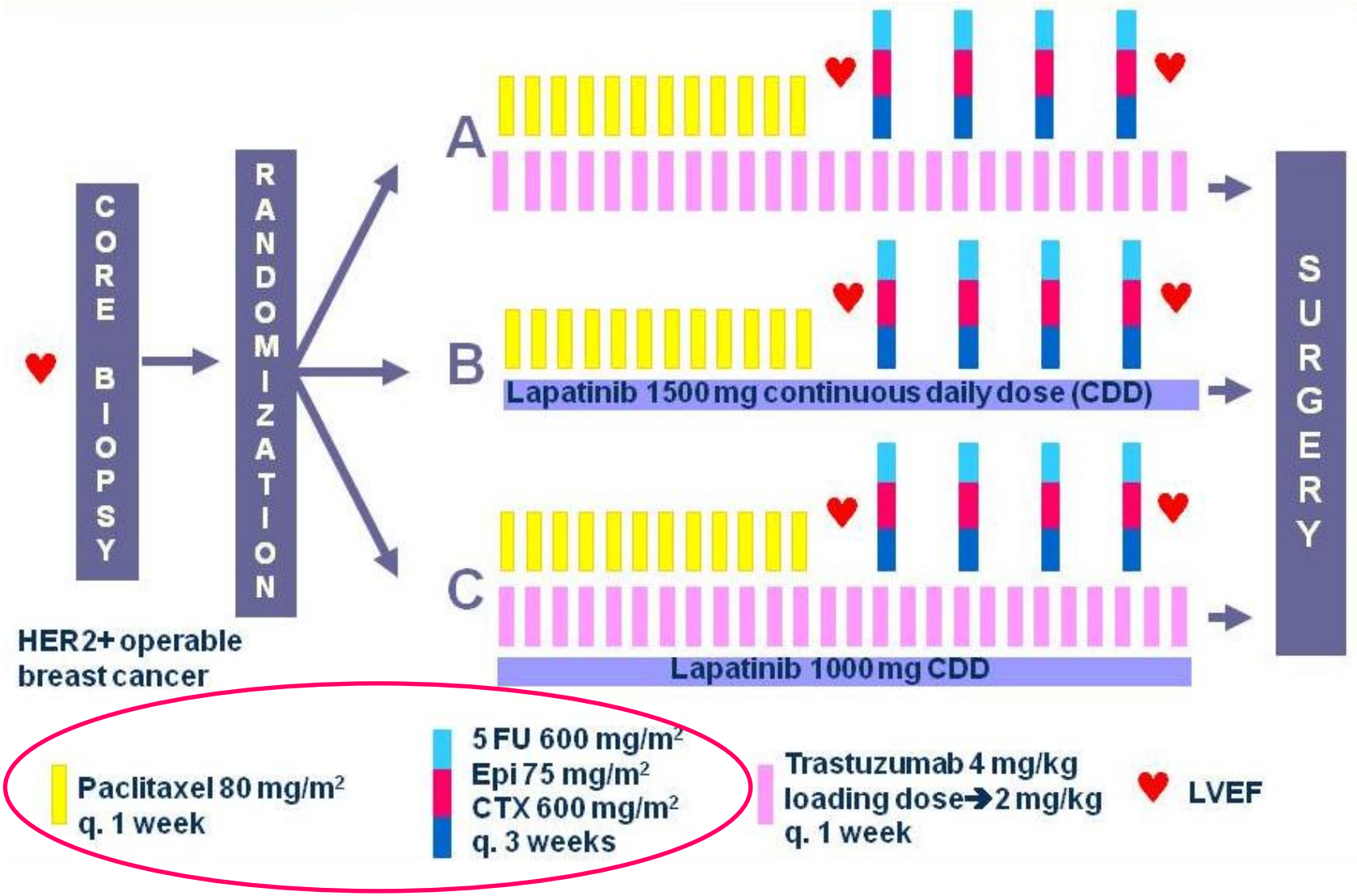
*Absence of invasive tumor in resected breast specimen and histologically negative axillary nodes.
†Relative to AC → WP + T regimen.

- **Similar results for dual blockade**
- **No significant difference between T and L**

Robidoux A, et al. ASCO 2012. Abstract LBA506.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

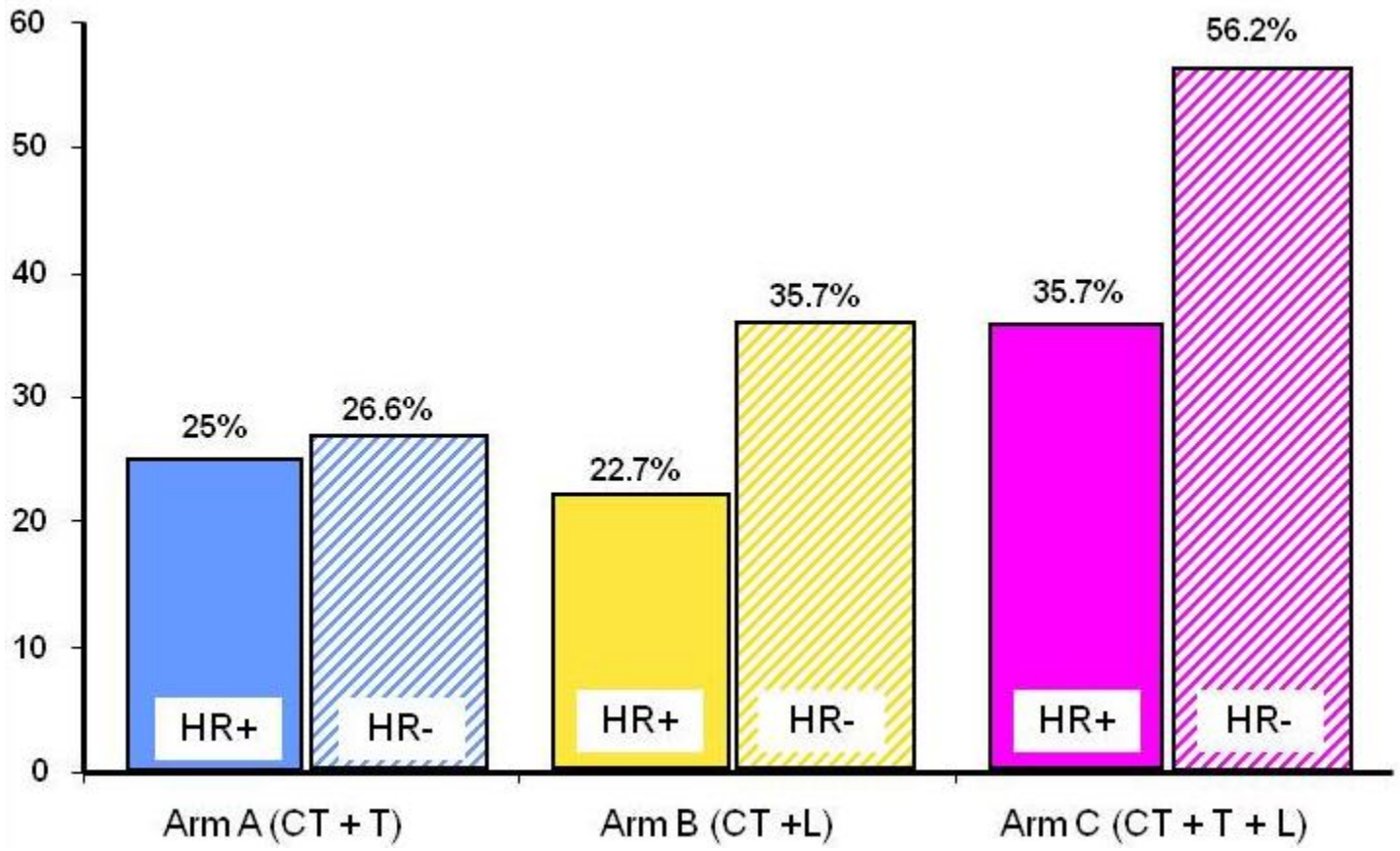
CherLob study plan



Guarneri, V et al. ASCO 2011 Abst 507

Breast & axillary pCR rate by HR

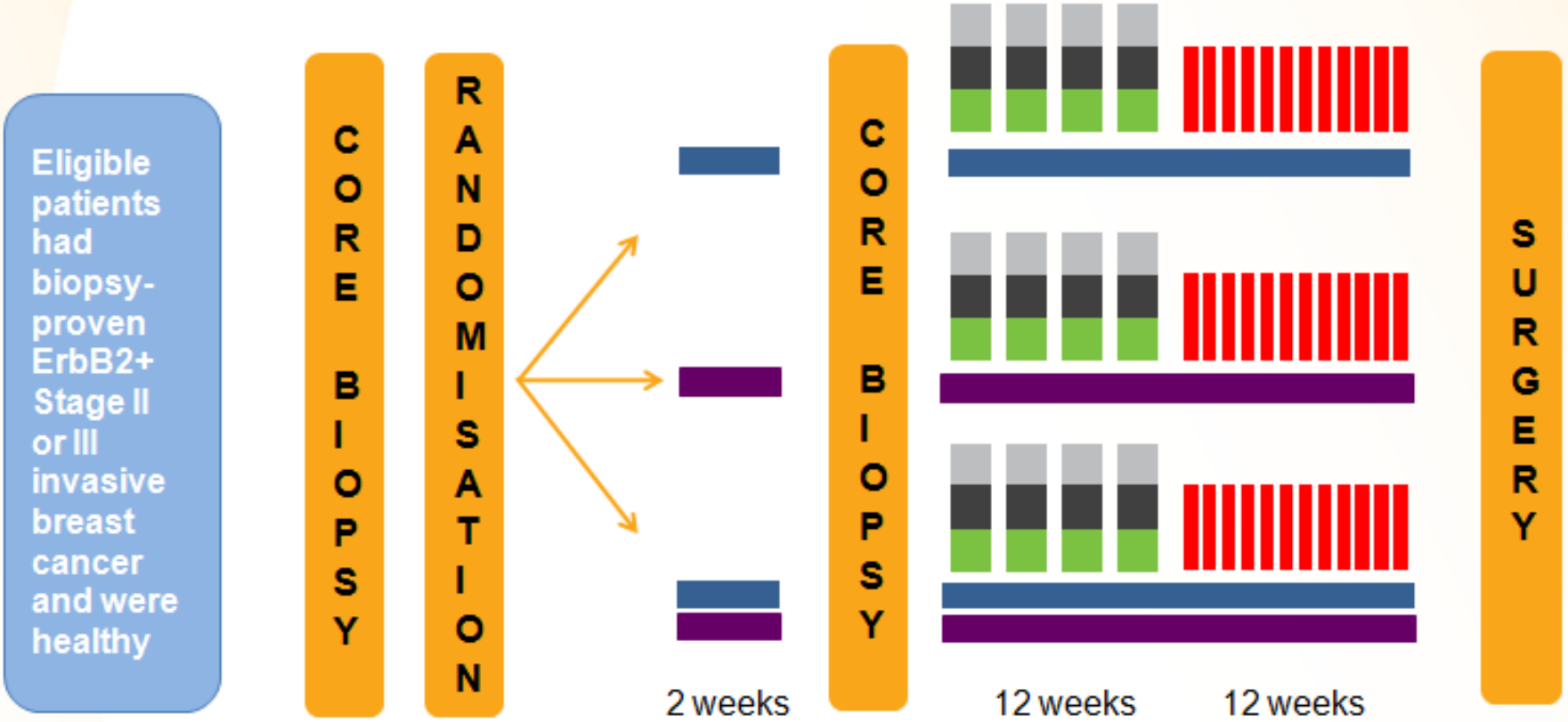
- Similar results for dual blockade
- Different results for T vs. L depending on HR status



T, trastuzumab; L, lapatinib; T+L, trastuzumab plus lapatinib

Guarneri, V et al. ASCO 2011 Abst 507

Neoadjuvant lapatinib and trastuzumab prior to and during chemotherapy: study design

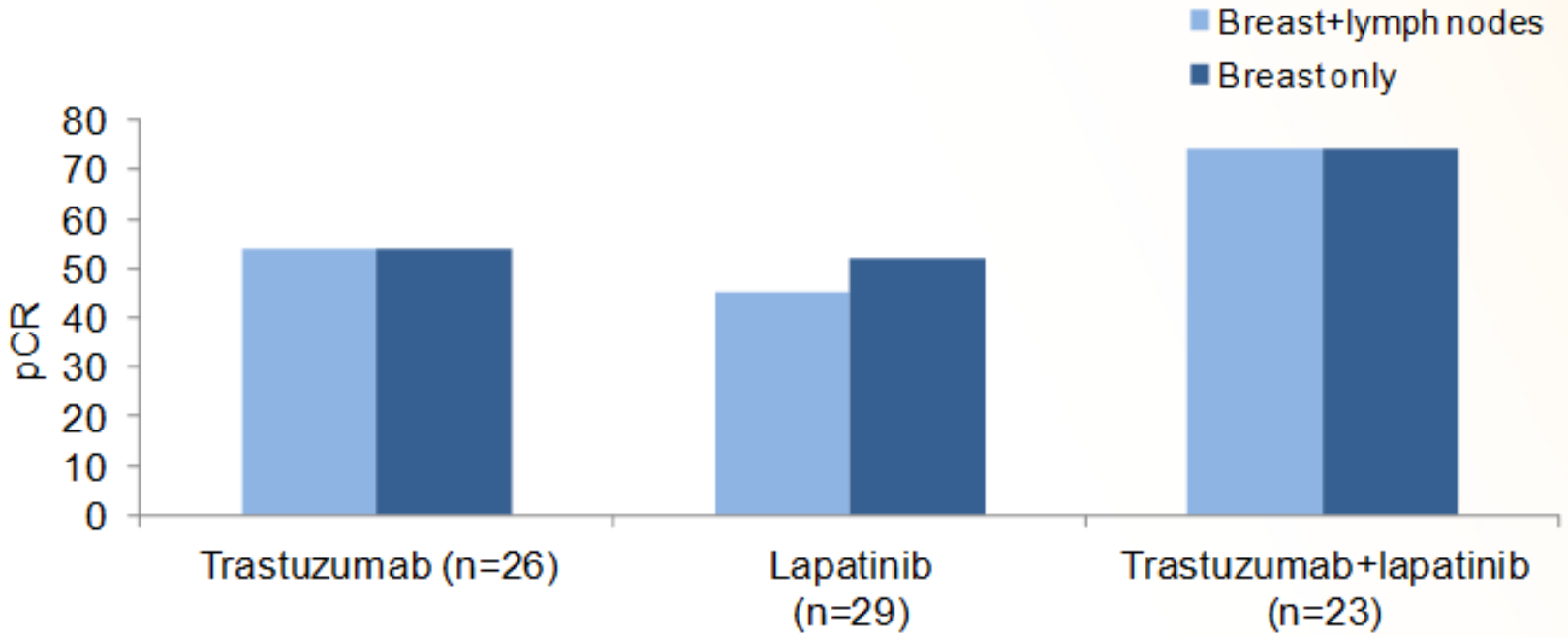


C, cyclophosphamide; E, epirubicin; F, 5-fluorouracil; q, every; qd, once daily

Holmes *et al. J Clin Oncol* 2011;29(Suppl):506

oncology academy

Neoadjuvant lapatinib and trastuzumab prior to and during chemotherapy: pCR



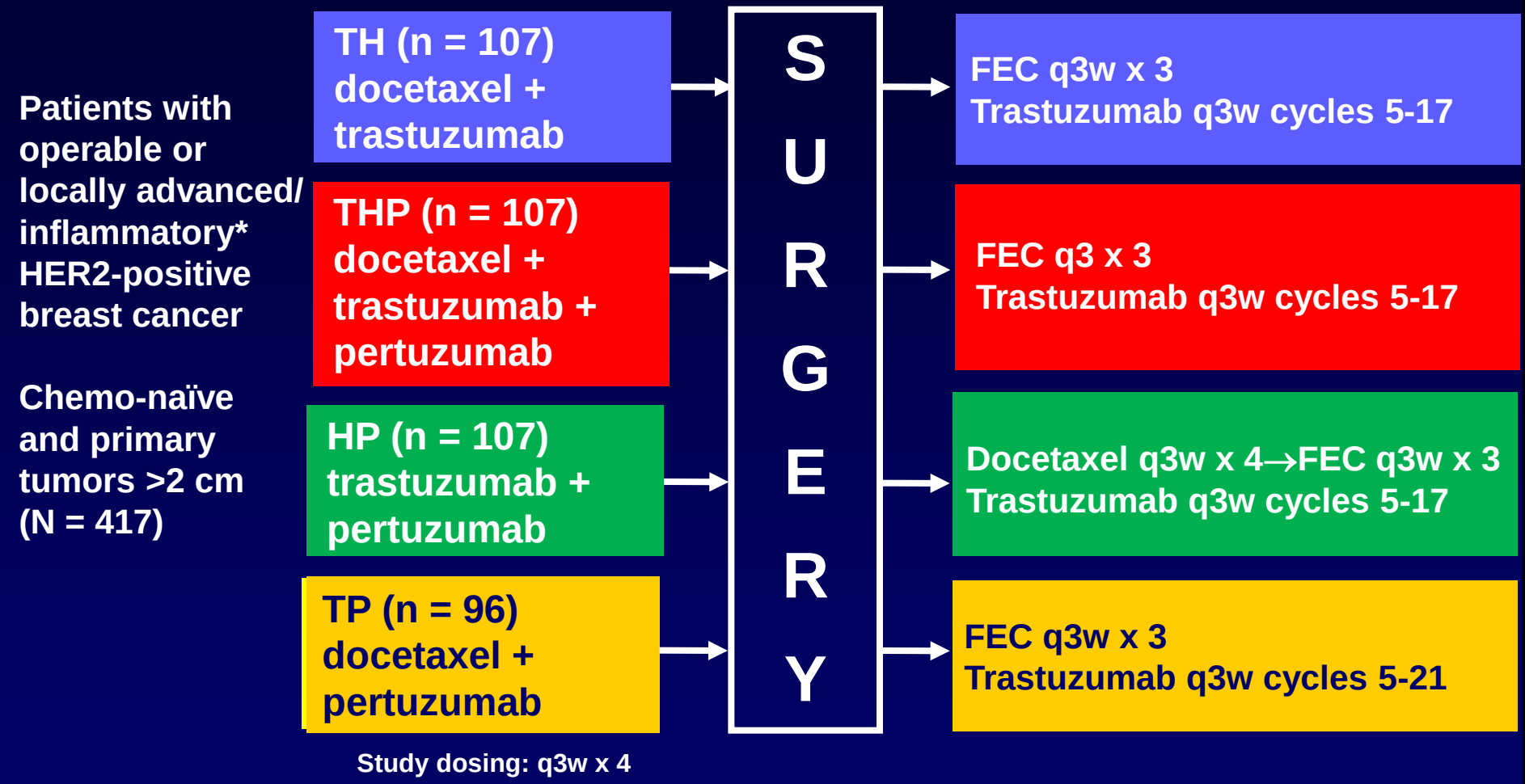
- **Similar results for dual blockade & T vs. L, with the "more commonly used" sequence A followed by Taxanes**

CI, confidence interval; pCR, pathological complete response:defined as absence of all invasive cancer in breast and lymph nodes

Holmes *et al. J Clin Oncol* 2011;29(Suppl.):506

oncology academy

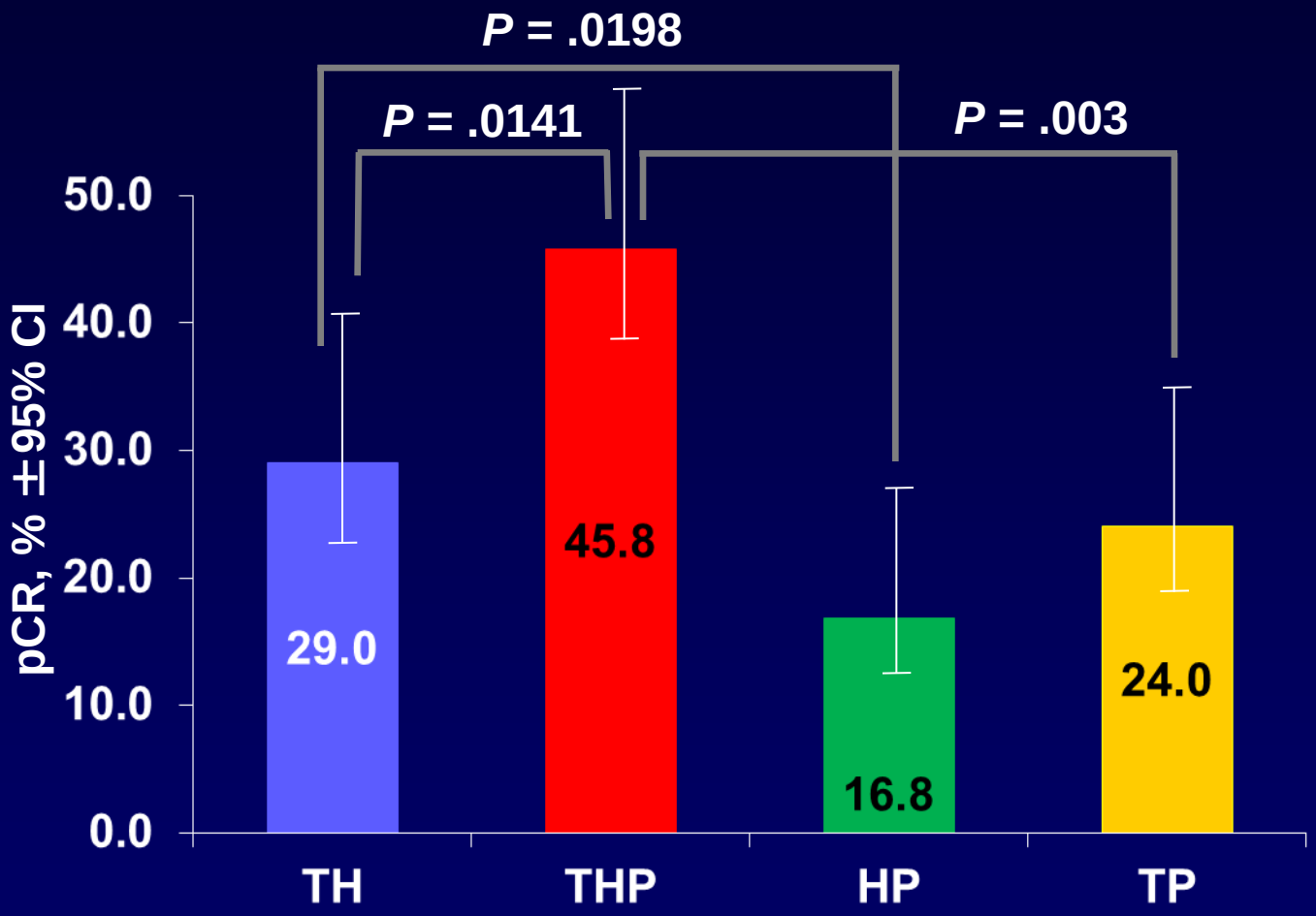
NeoSphere Study Design



BC, breast cancer; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel
*Locally advanced = T2-3, N2-3, M0 or T4a-c, any N, M0; operable = T2-3, N0-1, M0; inflammatory = T4d, any N, M0

Gianni L, et al. *Cancer Res.* 2010;70(24 Suppl): Abstract S3-2.

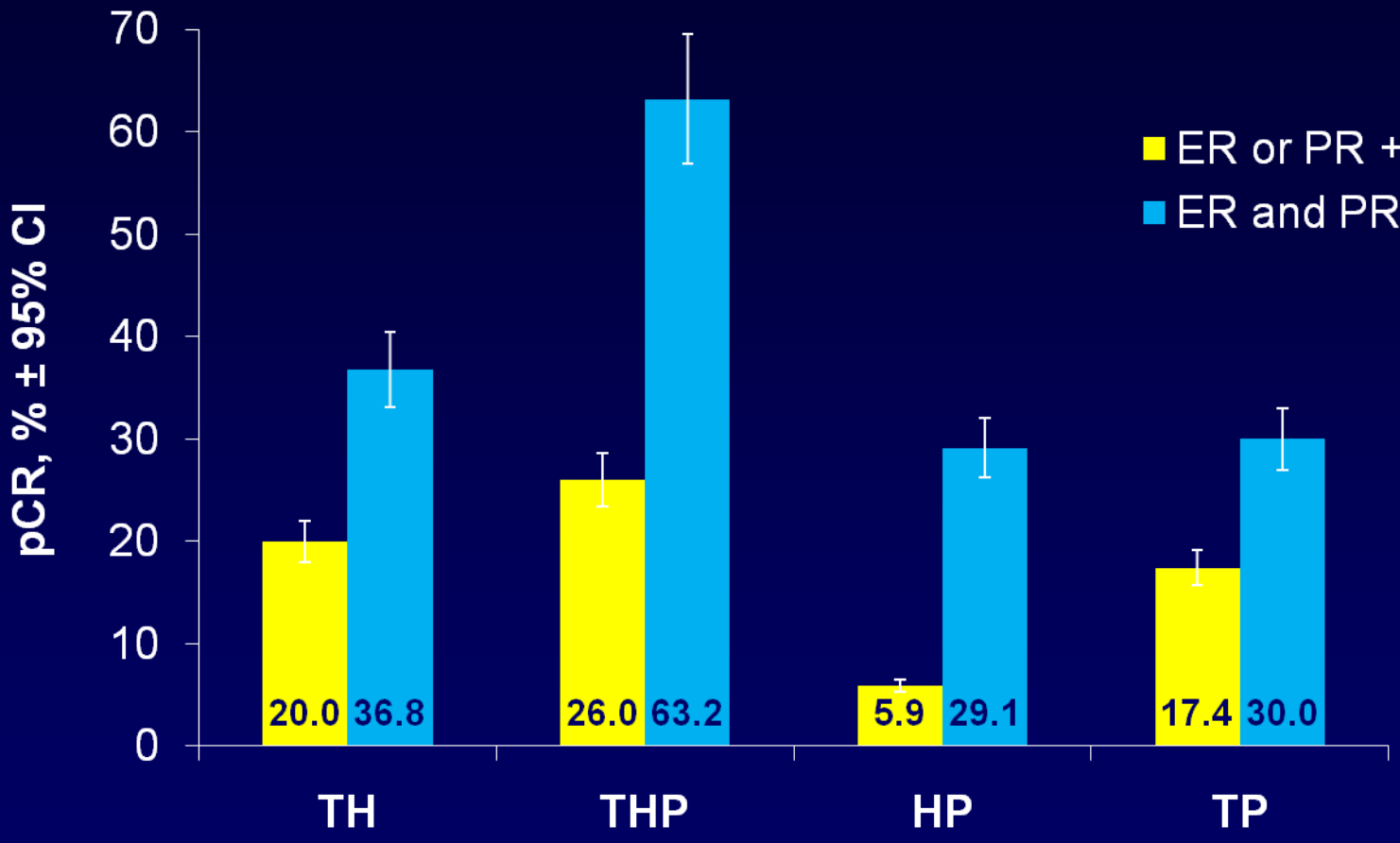
NeoSphere: pCR Rates (ITT Population)



CI, confidence interval; H, trastuzumab; P, pertuzumab; pCR, pathologic complete response; T, docetaxel

Gianni L, et al. *Cancer Res.* 2010;70(24 Suppl): Abstract S3-2.

NeoSphere: pCR and HR Status

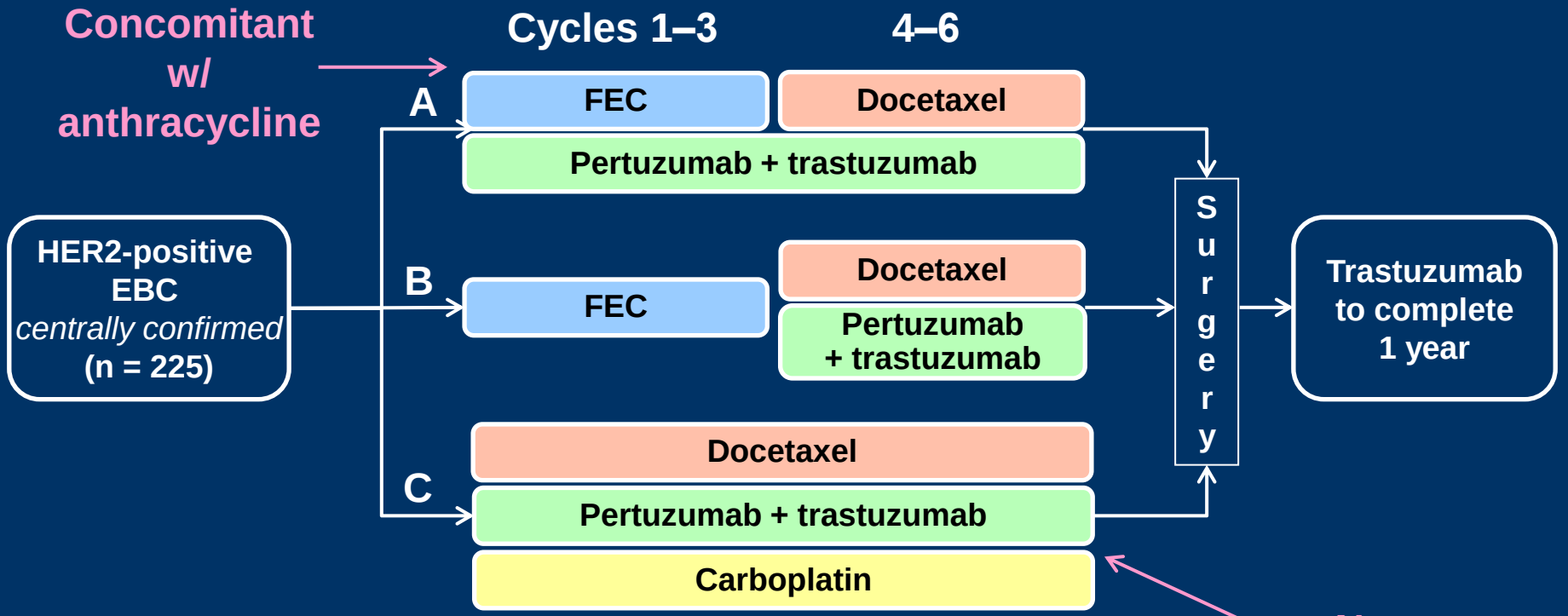


CI = confidence interval; H = trastuzumab; HR = hormone receptor; P = pertuzumab; pCR = pathologic complete response; T = docetaxel

Gianni L, et al. *Cancer Res.* 2010;70(24 Suppl): Abstract S3-2.

TRYPHAENA Ph 2 STUDY

Primary endpoint: cardiac safety
2ary endpoints: Toxicity, pCR, RR, BCS rate, DFS, OS



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

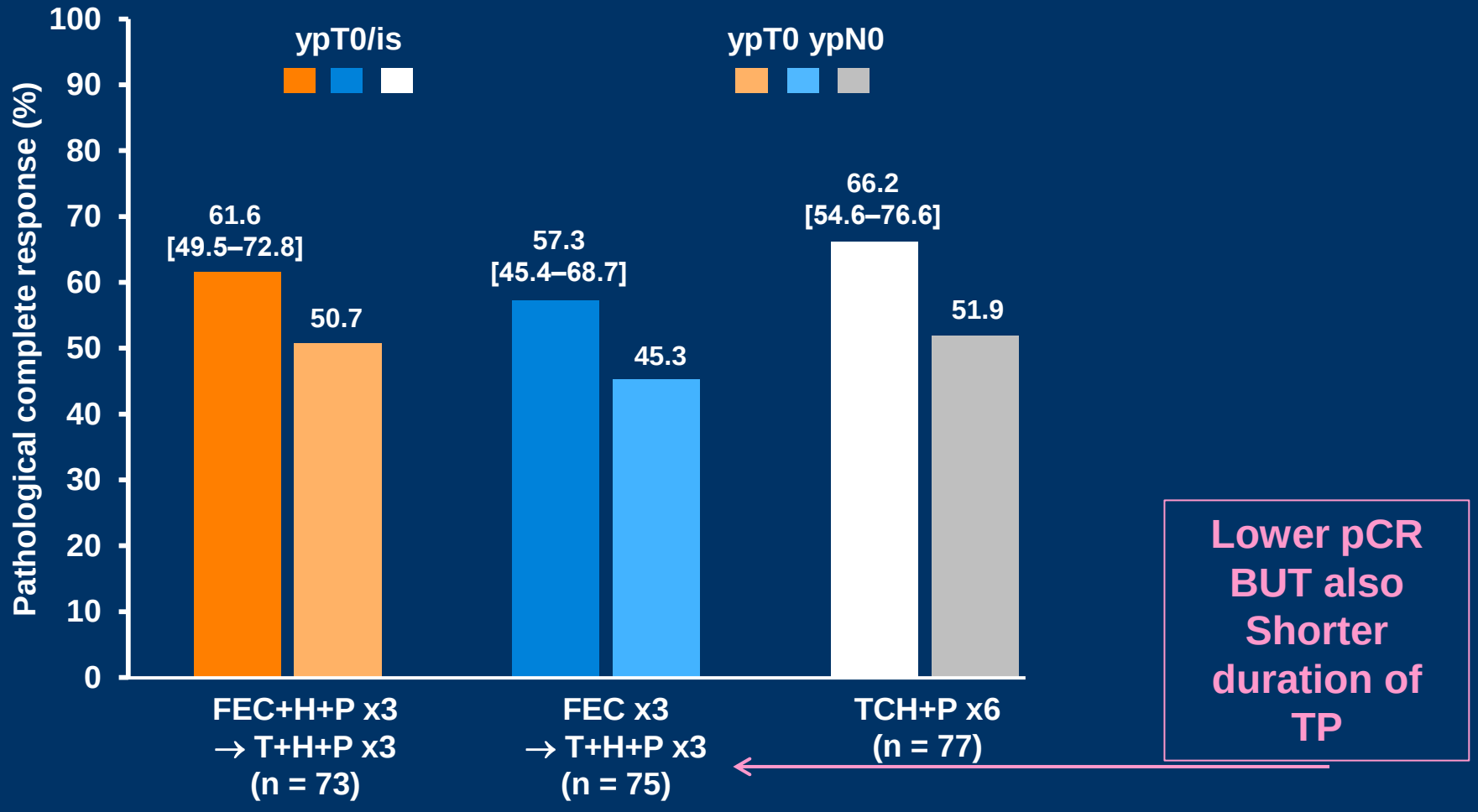
Cardiac events in the treatment period

	FEC+H+P x3 → T+H+P x3 n = 72	FEC x3 → T+H+P x3 n = 75	TCH+P x6 n = 76
Symptomatic LVSD (grade ≥3), n (%)	–	2 (2.7)	1 (1.3)
LVSD (all grades), n (%)	5 (6.9)	3 (4.0)	5 (6.6)
LVEF decline ≥10% points from baseline to <50%, n (%)	5 (6.9)	5 (6.7)	5 (6.6)

Primary endpoint: cardiac safety
NO SIGNIFICANT DIFFERENCES (safe to combine with A)

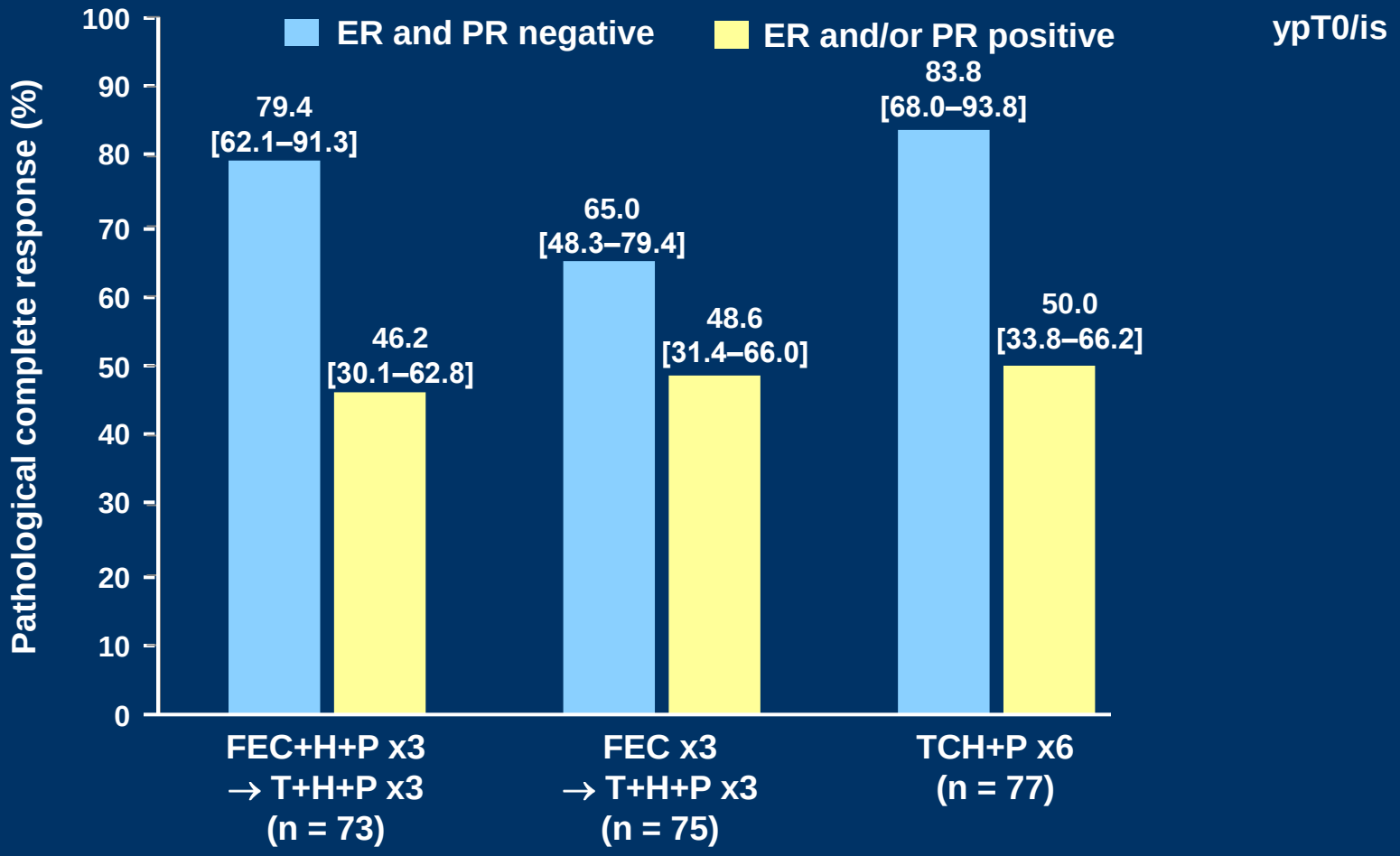
FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

Pathological complete response



FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

Pathological complete response by hormone receptor status



ER, estrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; PR, progesterone receptor; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

Neoadjuvant therapy for HER-2+ breast cancer

- The role of neoadjuvant trastuzumab
- Anti-HER-2 agent in neoadjuvant or adjuvant setting?
- Other anti-HER-2 agents
- Dual blockade
- **Which chemotherapy?**
- Biomarkers (example: p95)

Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2009

A. Goldhirsch[1,2*], J. N. Ingle[3], R. D. Gelber[4], A. S. Coates[5], B. Thürlimann[6], H.-J. Senn[7] & Panel members[†]

[1]International Breast Cancer Study Group, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; [2]European Institute of Oncology, Milan, Italy; [3]Breast Cancer Research Program, Mayo Clinic Cancer Center, Rochester, MN, USA; [4]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA; [5]International Breast Cancer Study Group, School of Public Health, University of Sydney, Sydney, New South Wales, Australia; [6]Breast Center, Kantonsspital, St Gallen, Switzerland and [7]Tumor and Breast Center ZeTuP, St Gallen, Switzerland

''If indicated, the majority of the Panel considered that the neoadjuvant chemotherapy regimen should include both a taxane and an anthracycline and (for HER2-positive disease) an anti-HER2 drug. Thus, the choice of a regimen for adjuvant or neoadjuvant chemotherapy might be made using similar criteria.''

Goldhirsch A, et al. *Ann Oncol.* 2009;20(8):1319-1329.

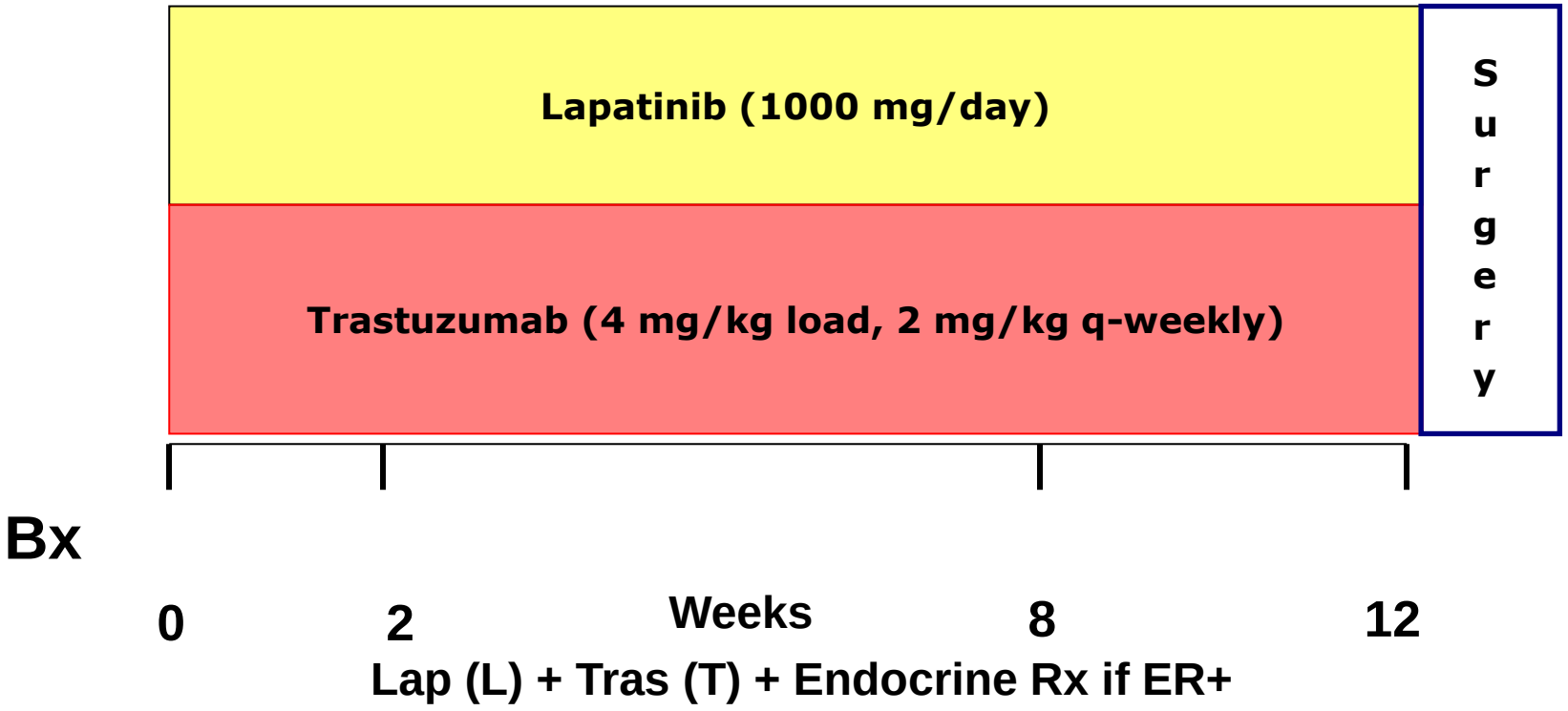
Neoadjuvant trials in HER2-positive B.C. Comparison of pCR-rates

	Neo-Sphere	Neo-Altto	NOAH	GeparQuinto
N	417	455	235	640
Mono-H	Doc+H	Pw+H	APH-PH-CMFH	ECH-DocH
Duration	12	12+6	30	24
$ypT_{0/is}$ ypN_0	21.5	27.6	38.0	45.0
Combo-H	Doc+HP	Pw+HL	n.a.	n.a.
$ypT_{0/is}$ ypN_0	39.3	46.9		

→ **Duration or use of anthracyclines add efficacy !**

Courtesy G. von Minckwitz, ASCO 2011

TBCRC 006: Neoadjuvant Lapatinib & Trastuzumab Without CT: Study Schema

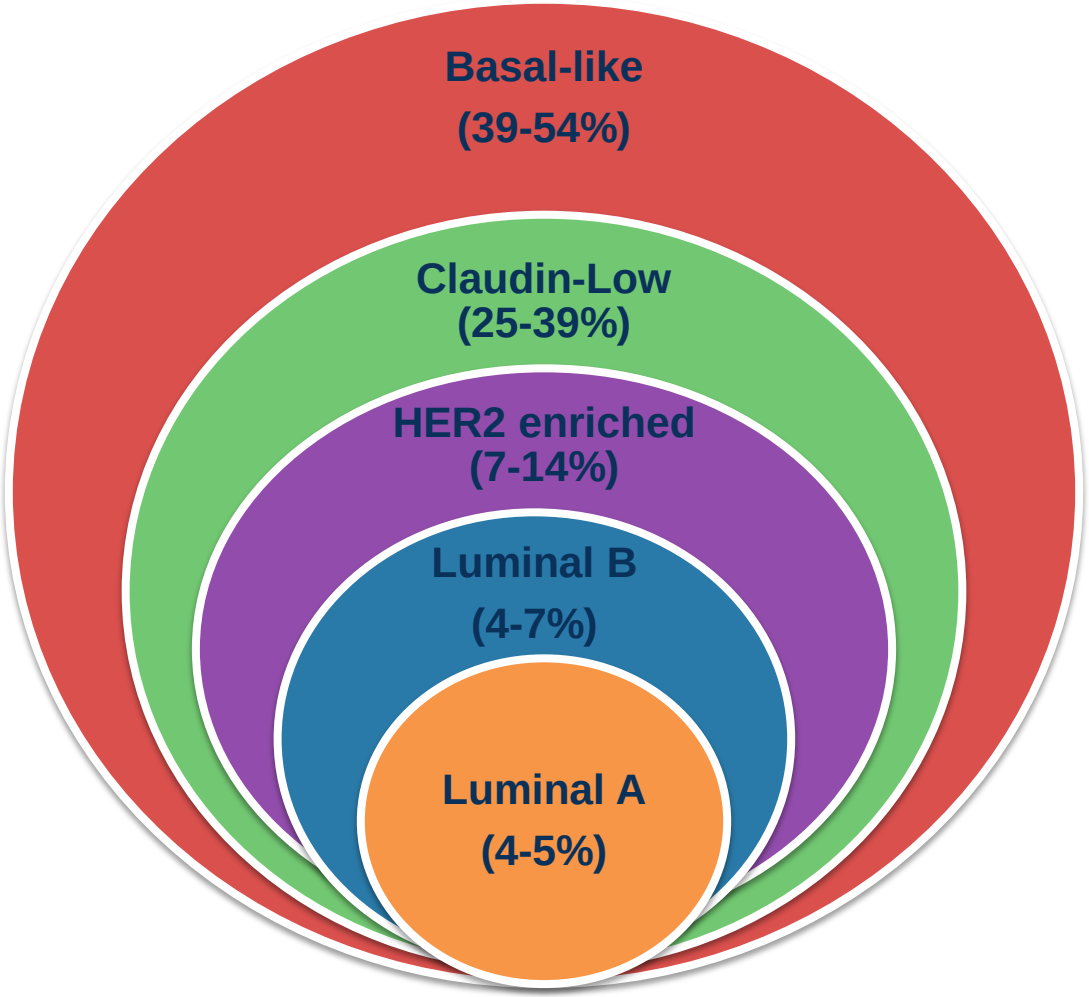


- pCR rates: 18/61 (30%)
  - ER pos: 8/39 (21%)
  - ER neg: 10/22 (46%)

Neoadjuvant therapy for TNBC

- **Which chemotherapy? Different than non-TNBC?**
- **Platinum compounds**

Heterogeneity of TNBC:
Data from the UNC337, NKI1295, MDACC133 databases



Basal-like
- Up to 19% are ER+

Claudin-low
- Up to 33% are ER+

Pratt et al, Breast Cancer Res, 2010

Courtesy H. Rugo, ASCO 2011

Pathologic Response to Anthracycline/Taxane by Subtype

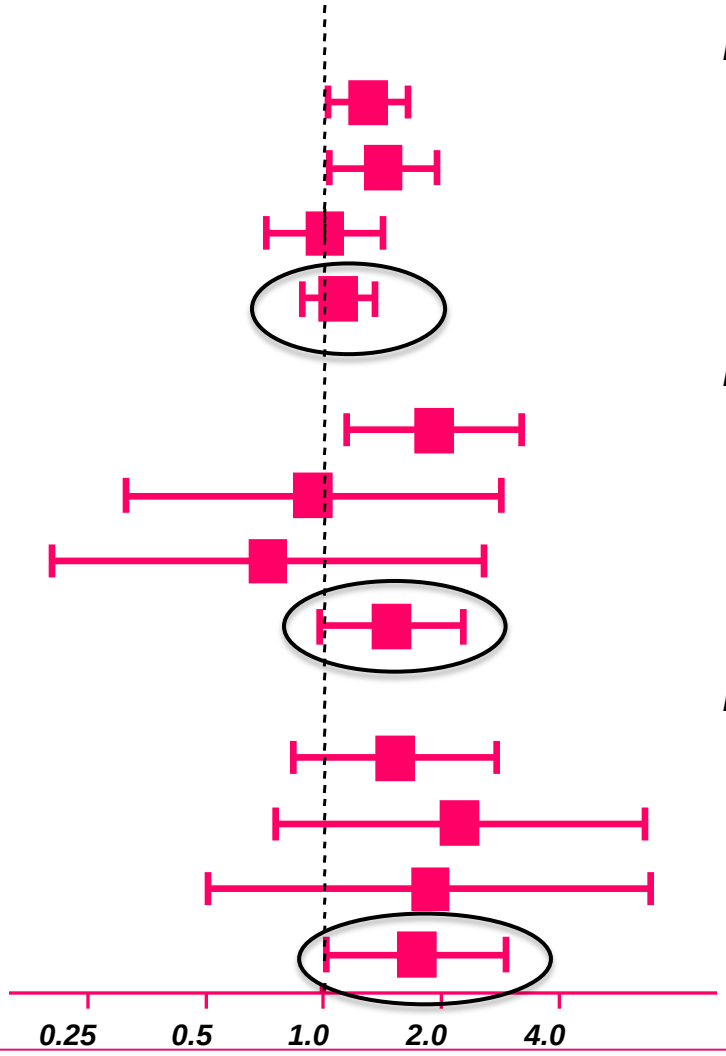
Overall pCR rate = 22% (82/369)

Classification	Residual disease	Pathologic complete response (pCR)
Basal-like	47 (58%)	34 (42%)
Claudin-low	29 (67%)	14 (33%)
HER2-enriched	31 (63%)	18 (37%)
LumA	110 (98%)	2 (2%)
LumB	56 (85%)	10 (15%)
Normal-like	13 (76%)	4 (24%)

Courtesy C. Perou

German neoadjuvant meta-analysis: Association of pCR with treatment characteristics stratified by HR & HER2 status*

Number of cycles (per 2 additional cycles)		***P=0.28***
HER2 - / HR +	***1.30 (1.02 to 1.65)***	
HER2 + / HR +	***1.42 (1.04 to 1.94)***	
HER2 + / HR -	***1.00 (0.71 to 1.41)***	
HER2 - / HR -	***1.09 (0.88 to 1.35)***	
Antracycline (high vs low dose)		***P=0.55***
HER2 - / HR +	***1.92 (1.14 to 3.21)***	
HER2 + / HR +	***0.94 (0.31 to 2.85)***	
HER2 + / HR -	***0.72 (0.20 to 2.58)***	
HER2 - / HR -	***1.49 (0.98 to 2.27)***	
Taxane (high vs low dose)		***P=0.92***
HER2 - / HR +	***1.52 (0.84 to 2.76)***	
HER2 + / HR +	***2.23 (0.75 to 6.61)***	
HER2 + / HR -	***1.87 (0.51 to 6.92)***	
HER2 - / HR -	***1.73 (1.02 to 2.94)***	



von Minckwitz et al, Breast Canc Res Treat (2010)

Platinum Sensitivity in BRCA1+/TNBC

Trial	Population	Regimen	N	pCR
Byrski	BRCA1+	Nonplatinum	90	14 (16%)
	BRCA1+	CDDP 75mg/m^2 x4	12	10 (83%)
Silver	Sporadic TNBC	CDDP 75mg/m^2 x4	26	4 (15%)
	BRCA1+	" "	2	2 (100%)
Ryan	Sporadic TNBC	CDDP 75mg/m2 x4 + bevacizumab 15 mg/kg q3wk x3	51	8 (16%)

- Neoadjuvant trials:
  - Retrospective trial suggests exquisite sensitivity in BRCA1+
  - Prospective trial in TNBC less clear
- Metastatic TNBC:
  - BALI-1 control arm cisplatin only – 10% RR

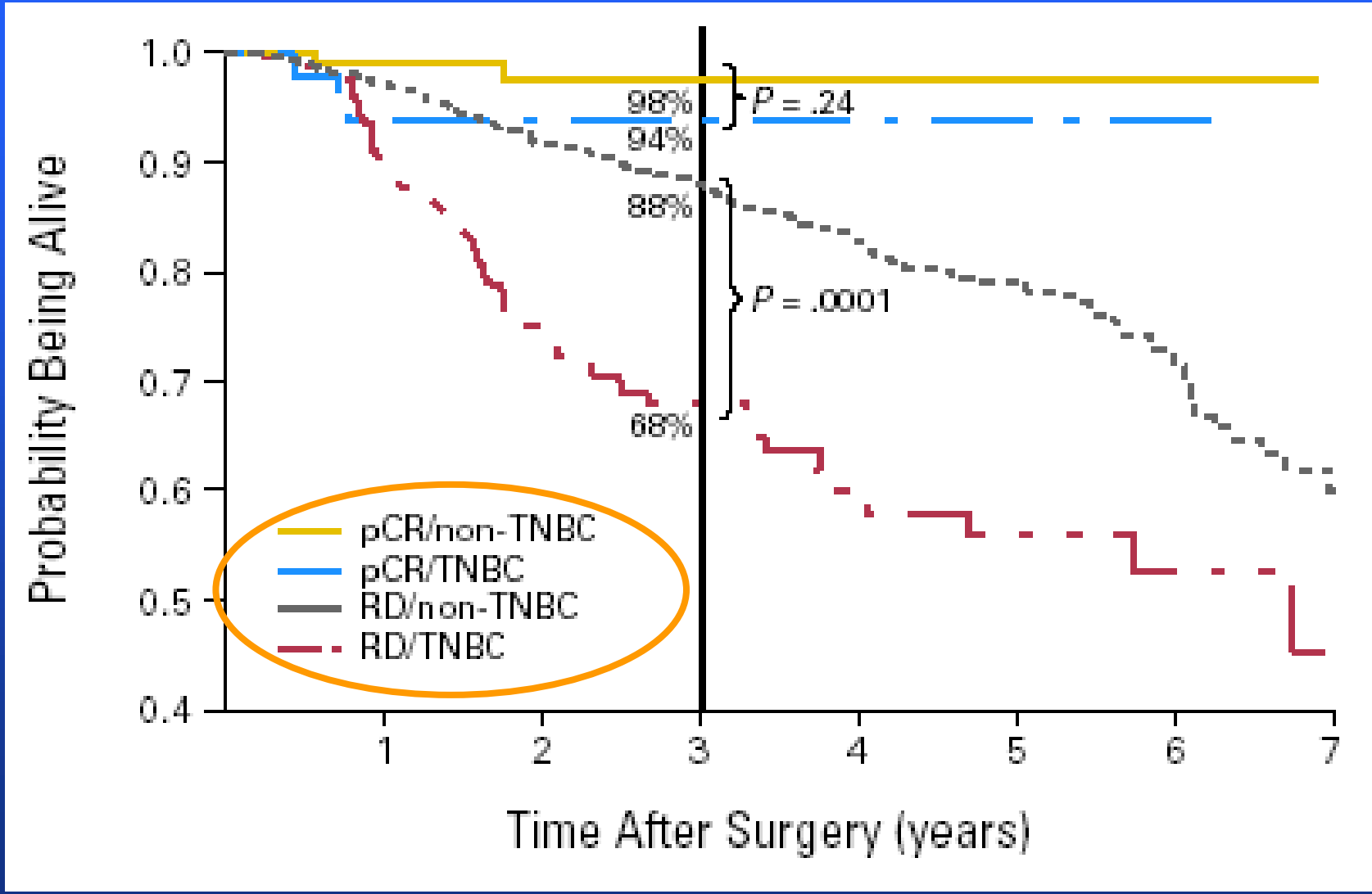
Byrski T, et al. *J Clin Oncol*. 2010;28(3):375-379. Silver DP, et al. *J Clin Oncol*. 2010;28(7):1145-1153. Ryan PD, at al. *J Clin Oncol.* 2009;27(15S): Abstract 551. Baselga ESMO 2010; Isakoff SABCS 2010

Neoadjuvant & Adjuvant Platinum CT regimens for TNBC

- **Very small number of patients**
- **Response to Platinum is mostly in BRCA+ TNBC**

- **Currently, there is no preferred standard form of chemotherapy for triple-negative breast cancer, and treatment should be selected as it is for other cancer subtypes.**

Overall survival as a function of response to neoadjuvant PCT



Liedtke C et al, J Clin Oncol, 2008, 26:1275

I-SPY 2 TRIAL

Learn, Drop, Graduate, and Replace Agents Over Time

Patient is on Study

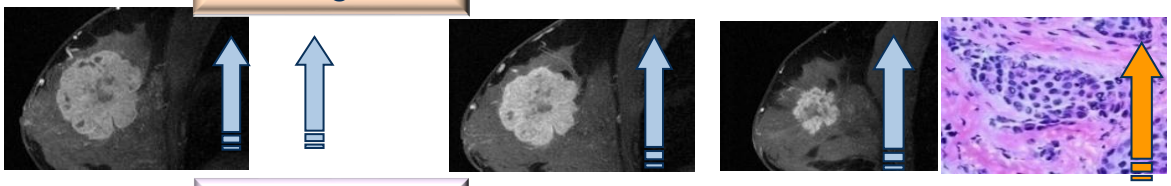
HER 2 (+)

Randomize

- **Paclitaxel+ Trastuzumab**
- **Paclitaxel + Trastuzumab* + New Agent A**
- **Paclitaxel + Trastuzumab* + New Agent B**
- **Paclitaxel + Trastuzumab* + New Agent F**

AC → Surgery

Learn and adapt from each patient as we go along



HER 2 (–)

Randomize

- **Paclitaxel**
- **Paclitaxel + New Agent F**
- **Paclitaxel + New Agent GH**
- **Paclitaxel + New Agent E**

AC → Surgery

Key

- MRI
- Residual Disease (Pathology)

**Investigational agent may be used in place*

Courtesy H. Rugo, ASCO 2011

BACK-UP

RECENT GUIDANCE DOCUMENT FROM FDA

- **Preoperative trials with pathologic complete response can, in selected circumstances, can be used for accelerated approval**
- **Trials evaluating clinically significant endpoints (DFS, OS) must be planning/pending**
- **Expectation is that triple negative breast cancer will be first area explored**
- **Guidance was well received by academic, advocate, and pharma communities**
- **Potentially major implications for drug development**

Courtesy E. Winer

pCR IS NOT YET AN ENDPOINT FOR DRUG APPROVAL OR PRACTICE CHANGE

- **Path CR is consistently associated with excellent outcome**
- **Improvements in path CR have not always associated with better DFS/OS**
- **Failure to achieve path CR is associated with variable outcome**
- **Will more effective anti-HER-2 therapy in neoadjuvant setting lead to long term benefit?**

Courtesy E. Winer