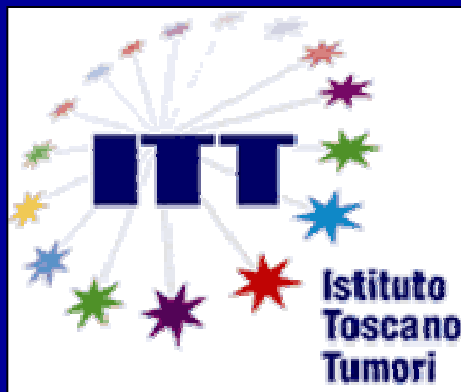


# Neo-adjuvant and adjuvant treatment for HER-2+ breast cancer

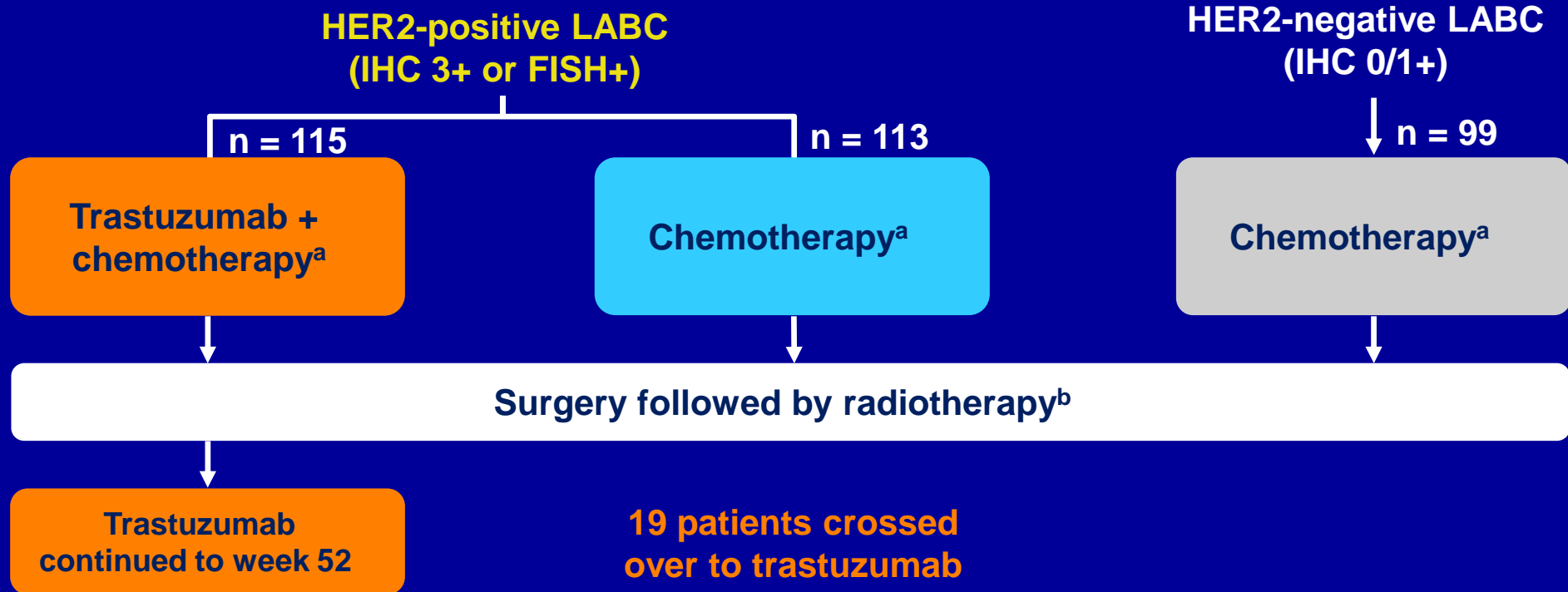
Angelo Di Leo



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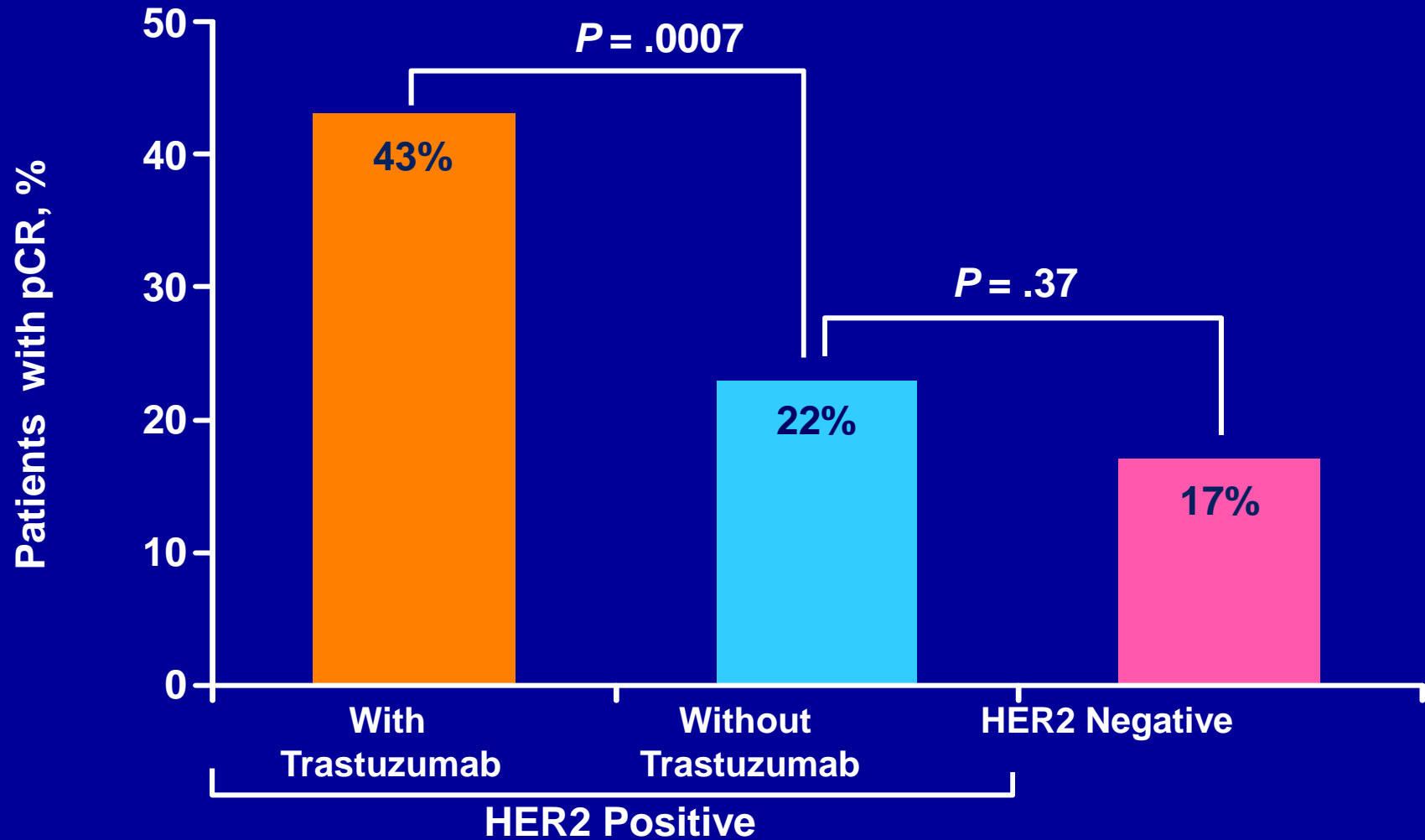
# NOAH: Phase III, Open-Label Trial of Neoadjuvant Trastuzumab



<sup>a</sup>Chemotherapy: Doxorubicin, paclitaxel x 3 → paclitaxel x 4 → cyclophosphamide, methotrexate, 5-fluorouracil x 3

<sup>b</sup>Hormone receptor-positive patients received adjuvant tamoxifen  
FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry

# NOAH Trial: Trastuzumab Improves pCR Rates in Breast Patients with HER2-Positive LABC

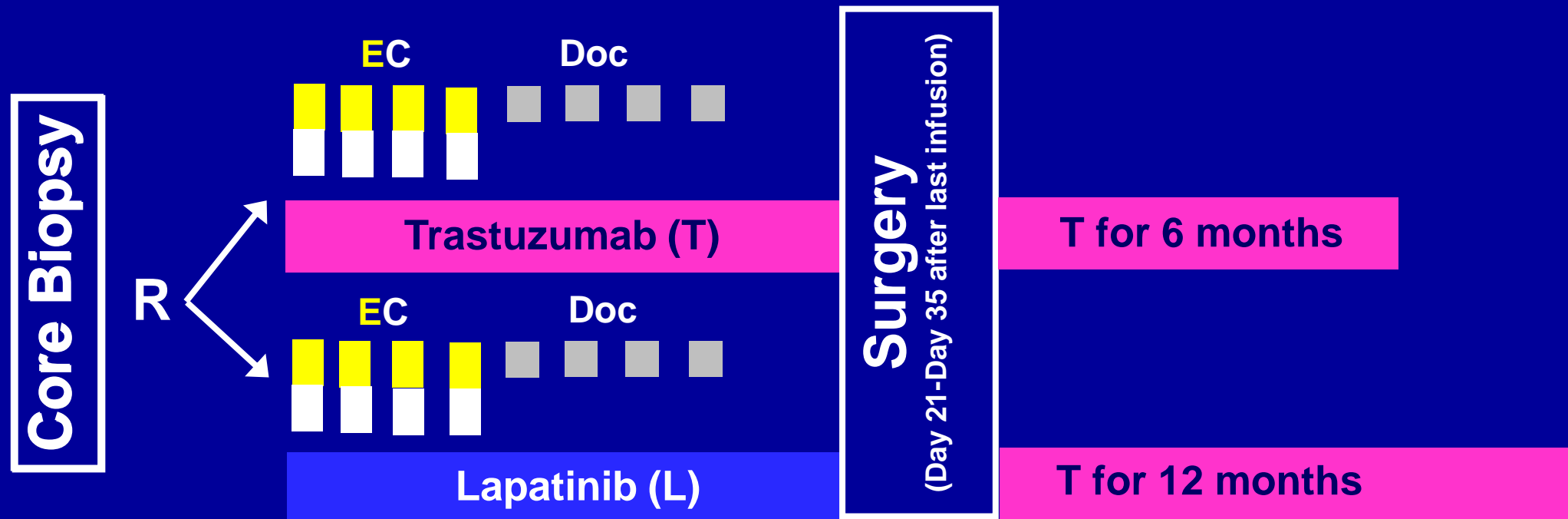


# The NOAH Trial: Main Comments

- 1) The study design cannot assess the superiority of a trastuzumab-based neoadjuvant treatment regimen over a trastuzumab-based adjuvant treatment regimen (no adjuvant trastuzumab in the HER2-positive control arm)
- 2) Potential advantages deriving from the combination of trastuzumab with neoadjuvant chemotherapy:
  - Synergism trastuzumab-chemotherapy → improve local and systemic control?
  - Identify patients who do not benefit.  
Problem: lack of treatments with proven efficacy in non-pCR patients

# GeparQUINTO

## HER2-Positive Study Design

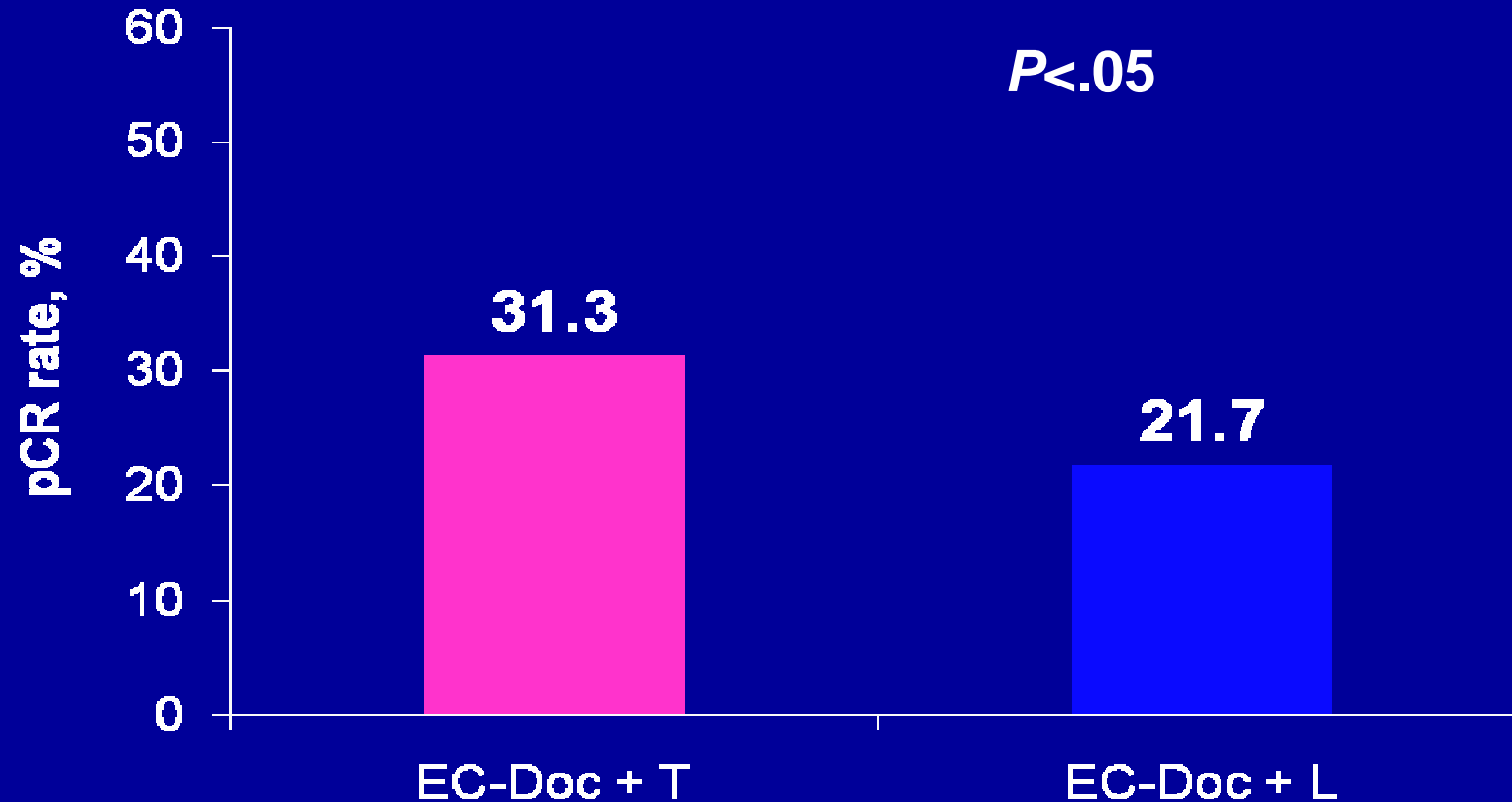


**E:** Epirubicin 90 mg/m<sup>2</sup>  
**C:** Cyclophosphamide 600 mg/m<sup>2</sup>  
**Doc:** Docetaxel 100 mg/m<sup>2</sup>\* + G-CSF

**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

# 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.

# The GeparQUINTO Trial: Main Comments

- 1) Trastuzumab > Lapatinib in terms of pCR rate**
- 2) However Trastuzumab = Lapatinib if in the Lapatinib arm no dose-reduction or discontinuation**
  - Can we predict tolerability to Lapatinib?**
  - Shorter (< 24 wks) Lapatinib regimens?**
- 3) Is the Trastuzumab vs Lapatinib question the real issue?**

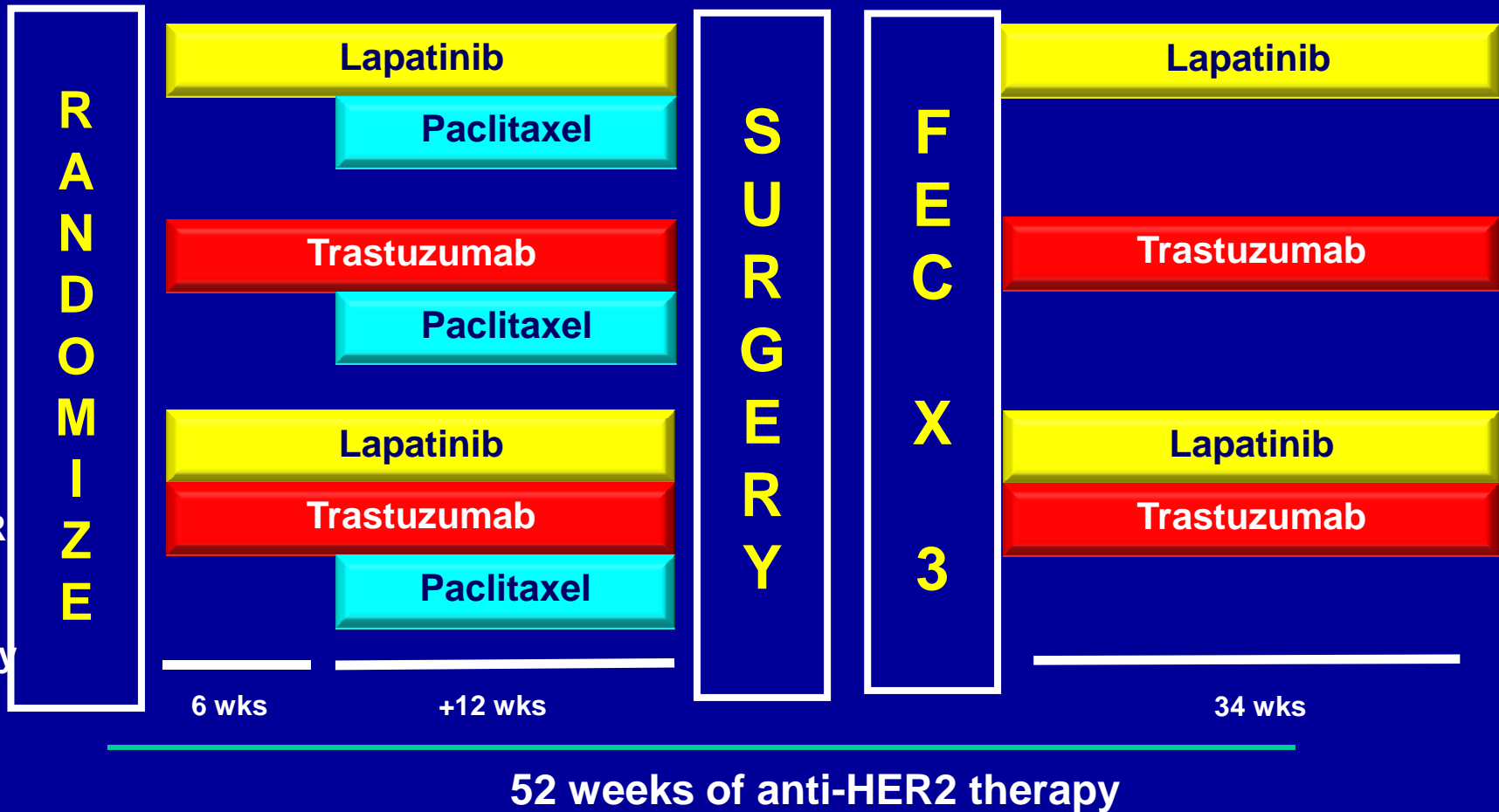
# NeoALTT0 Study Design

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

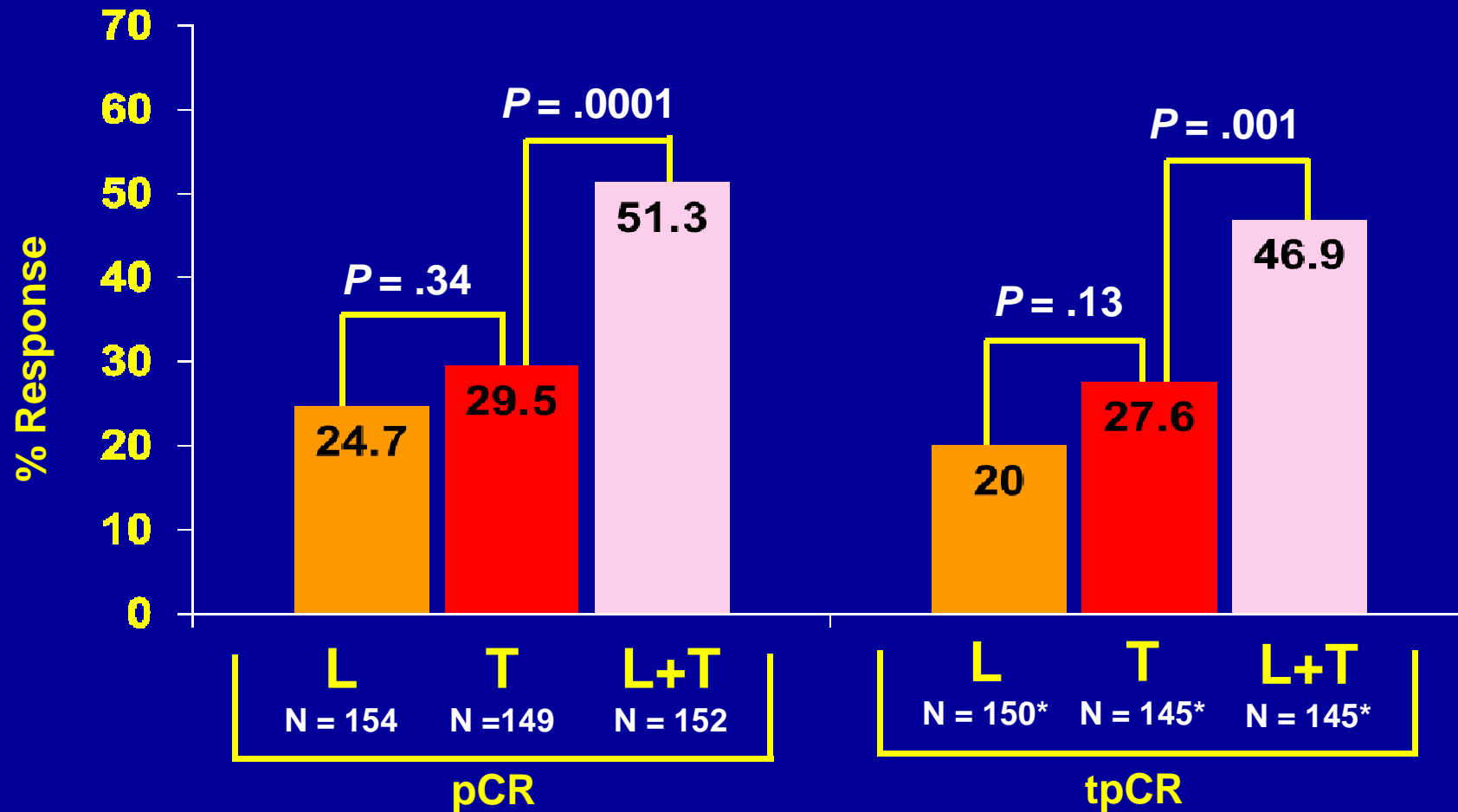
**N = 450**

## Stratification

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



# NeoALTT0 Efficacy: pCR and tpCR



**Pathologic Complete Response**

**Locoregional (total) pCR**

**\*Excludes 15 patients with nonevaluable nodal status**

L, lapatinib; pCR, pathologic complete response; T, trastuzumab;  
L+T, lapatinib plus trastuzumab

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

# Safety

Number (%) of Patients with Adverse Events  $\geq$ Grade 3

	L (N = 154)	T (N = 149)	L+T (N = 152)
Diarrhea	36 (23)	3 (2)	32 (21)
Hepatic*	20 (13)	2 (1)	13 (9)
Neutropenia	24 (16)	4 (3)	13 (9)
Skin disorders	10 (7)	4 (3)	10 (7)

- No major cardiac dysfunction
- One death in L+T immediately after end of treatment

L, lapatinib; T, trastuzumab

\*Includes 2 patients with Hy's law criteria in T, and 1 patient in L

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

# The Neo-ALTT0 Trial: Main Comments

- 1) Lapatinib + trastuzumab > trastuzumab in terms of pCR rate
- 2) Can similar results be observed when a sequential full-dose anthracycline-taxane regimen is combined to lapatinib-trastuzumab?
- 3) Objective response rate after the first 6 weeks of treatment:  
Lapatinib alone = 52.6%, trastuzumab alone = 30.2%,  $P < .001$

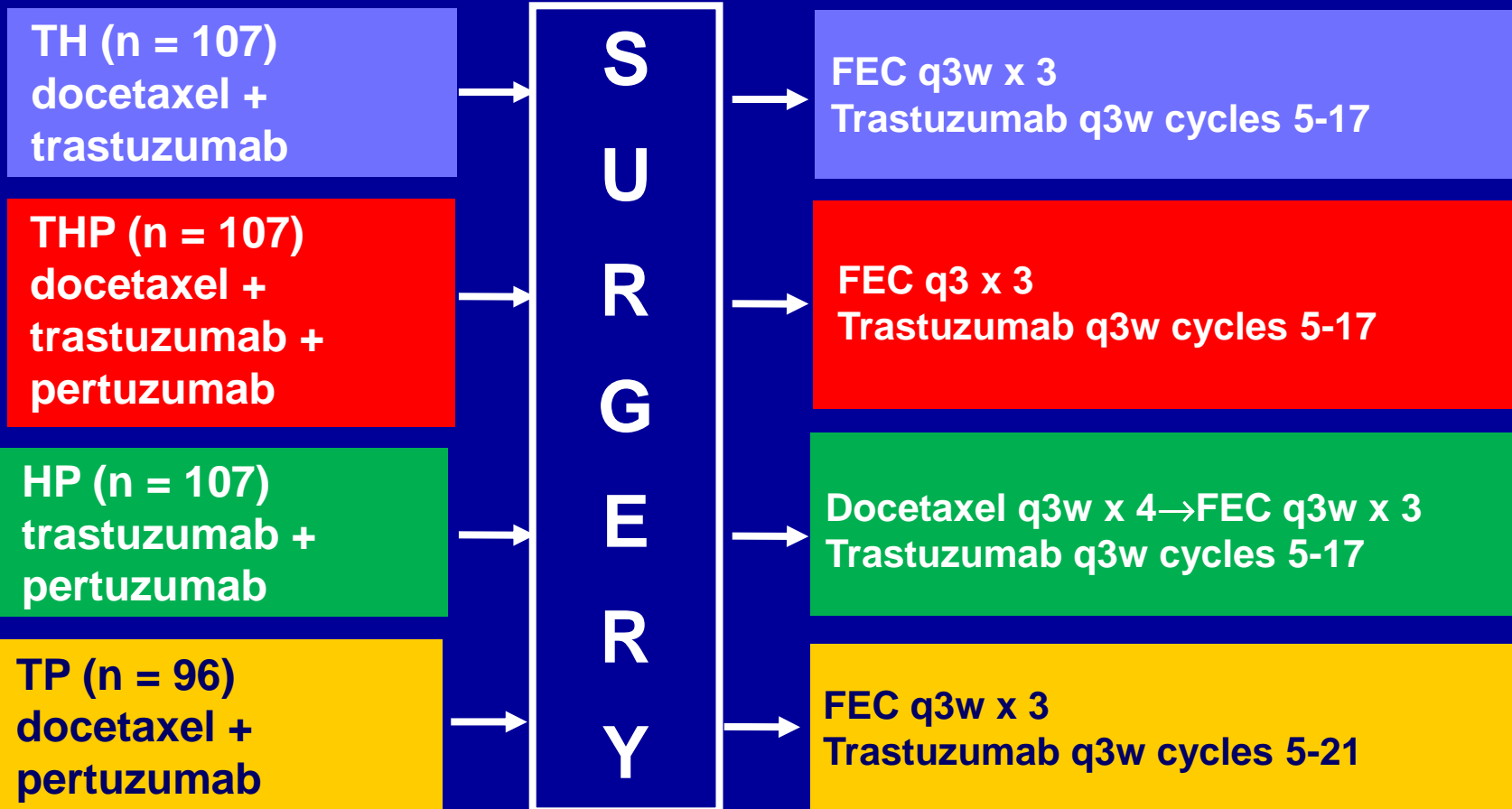
## Potential explanations:

- Lapatinib alone  $\longrightarrow$  full doses, no discontinuation
- More rapid response with L than with T ?
- Play of chance?

# NeoSphere Study Design

Patients with operable or locally advanced/  
inflammatory\*  
HER2-positive  
breast cancer

Chemo-naïve and  
primary tumors >2  
cm  
(N = 417)



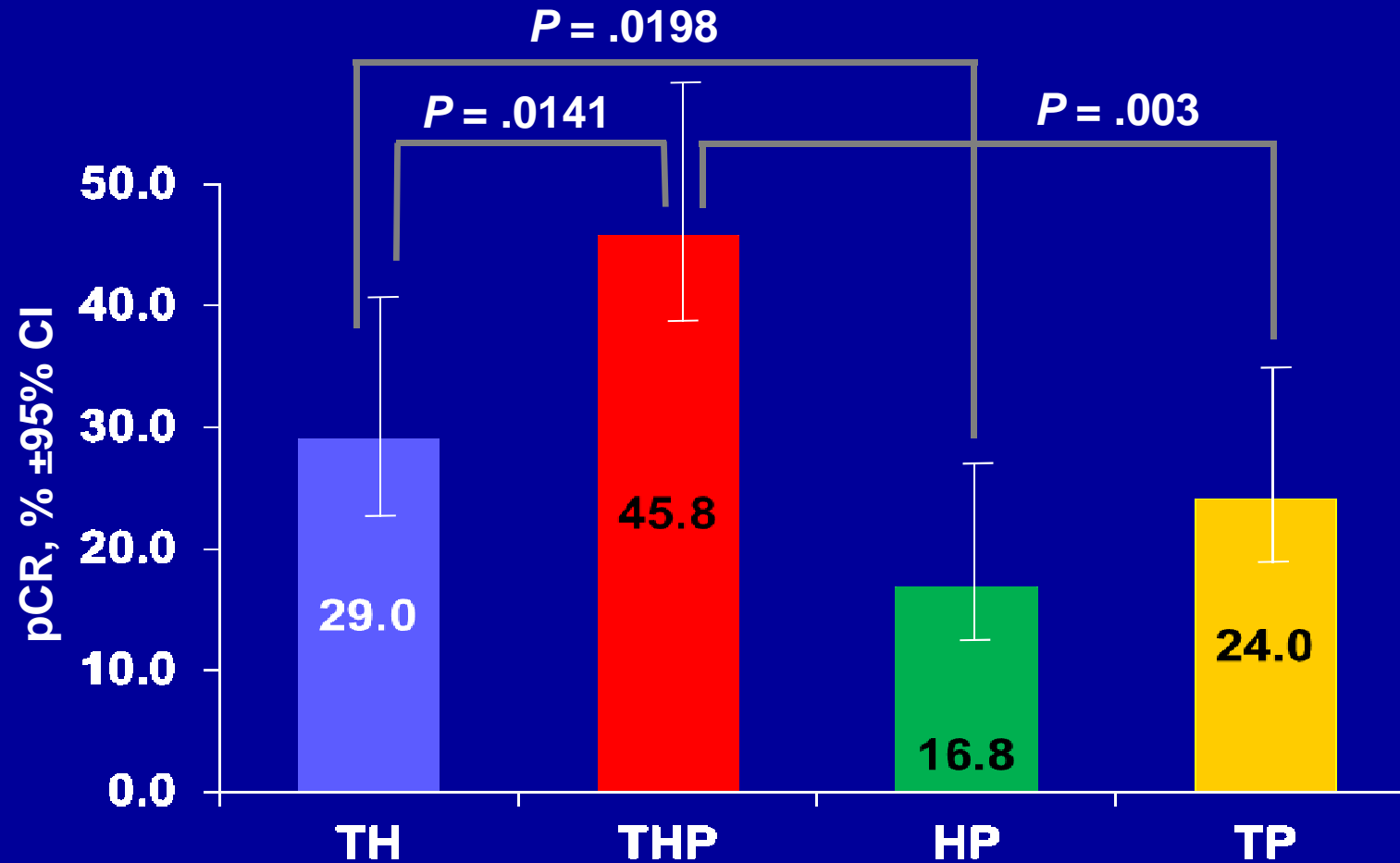
Study dosing: q3w x 4

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.

# The NeoSphere Trial: Main Comments

- 1) Pertuzumab – trastuzumab > trastuzumab in terms of pCR rate
- 2) Can similar results be observed when a sequential full-dose anthracycline-taxane regimen is combined to pertuzumab-trastuzumab?
- 3) Research questions:
  - Why PT more active in ER negative than in ER + patients?
  - Can we identify patients where no chemotherapy is needed to achieve a pCR?

**Adjuvant treatment  
of pT<sub>1</sub>pN0 HER-2 + disease**

# **Studies investigating clinical outcome of pT1pN0 tumors by HER-2 and hormone receptors (HRs) status.**

## **Methods**

- 7 retrospective studies reported between 2003 and 2010**
- Evaluation of disease- and distant disease-free survival by HER-2 and HER-2/HRs**
- HER-2 centrally evaluated in all studies**

## **Studies investigating clinical outcome of pT1pN0 tumors by HER-2 and hormone receptors (HRs) status. Results**

- **Overall 7,164 pts. with pT1pN0 tumors (median follow-up 4.5 - 12.4 yrs.)  
- 600 pts. with HER-2 + tumors**
- **% HER-2 + disease ranging between 7 and 10%**
- **Absolute risks of distant relapse  
- HER-2 + : 5 yrs.  $\pm$  10-15%, 10 yrs. 22-28%**
- **Increased risk of disease relapse if HER-2 + (hazard ratios ranging between 2.4 and 8.99)**
- **Two studies suggest a worse outcome for triple negative than for ER+/HER-2 negative tumors**

## **Studies investigating clinical outcome of pT1pN0 tumors by HER-2 and hormone receptors (HRs) status. Caveats and Conclusions**

- **Caveats**
  - **heterogeneity in adjuvant therapies**
  - **HRs status not always centrally revised**
  - **in 3 out of 7 studies pT1c tumors were eligible**
  - **only 2 out of 7 studies evaluate outcome by combination of HER-2 and HRs status**
- **“Take-home” messages**
  - **there is a substantial degree of concordance in considering HER-2 + patients with pT1pN0 tumors at increased risk of relapse compared to the HER-2 negative population (2 to 9 fold increase)**
  - **preliminary findings suggest that the increased risk of relapse may also be true for triple negative pT1pN0 tumors**

# Key question

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Is proportional benefit from adjuvant systemic therapies dependent on disease stage?

# Proportional benefits from systemic therapies are independent of nodal status

## Effects on recurrence

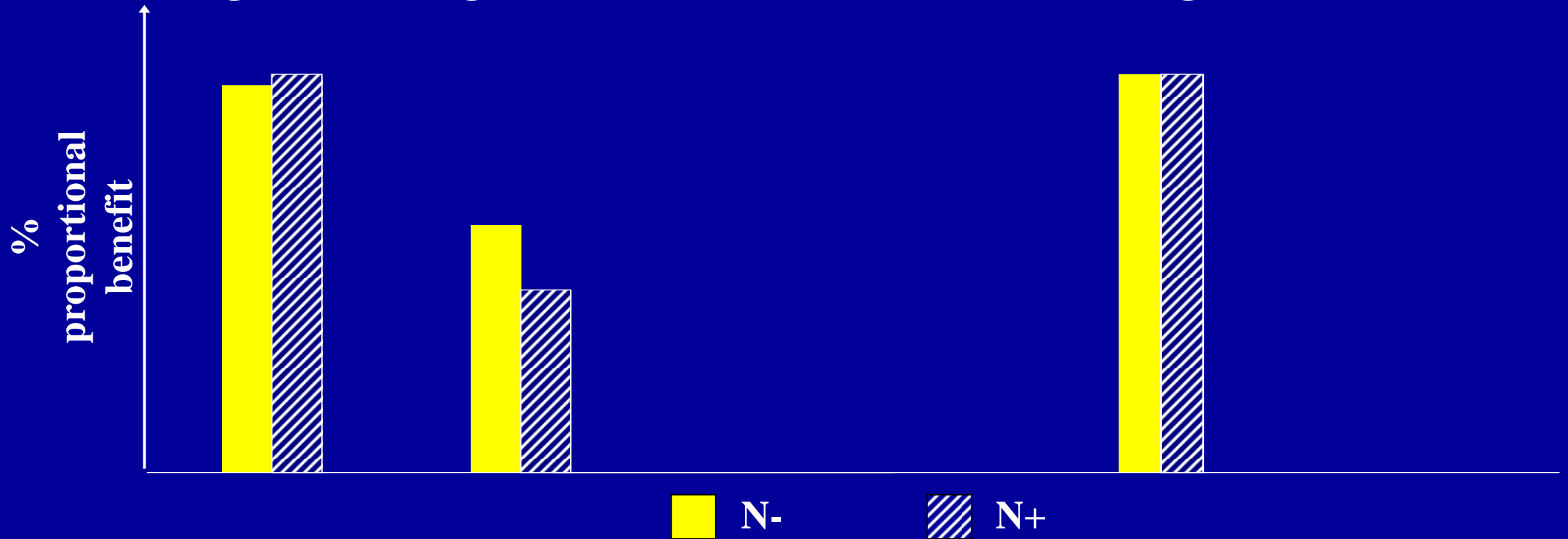
Polychemo vs. not

± 5 yrs. TAM vs. not in ER+ or uk

age <50

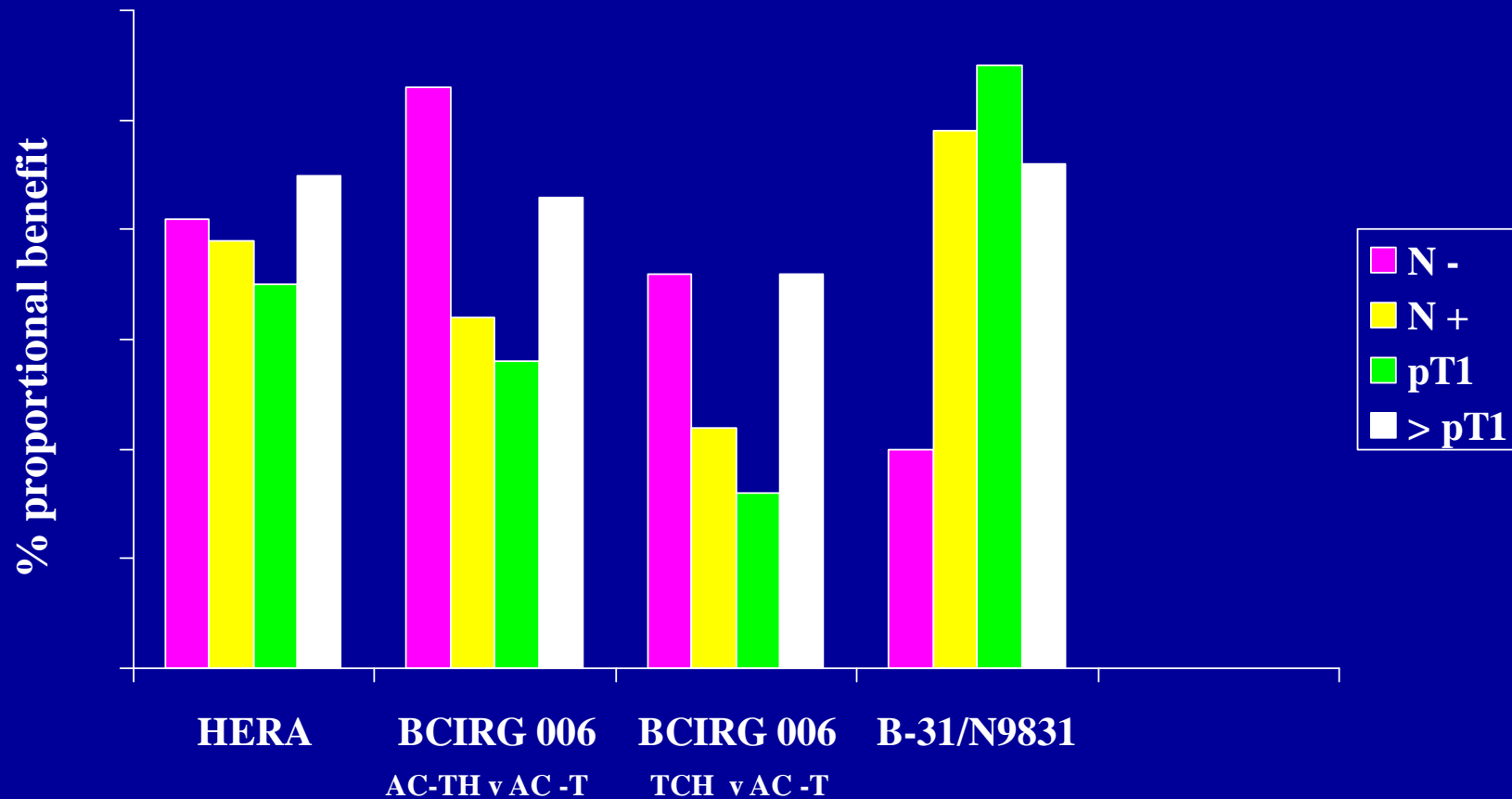
age 50-69

all ages



Similar findings when effects on breast cancer mortality are evaluated

# Proportional benefits on risk of recurrence from adjuvant trastuzumab seem to be independent of nodal status or tumor size

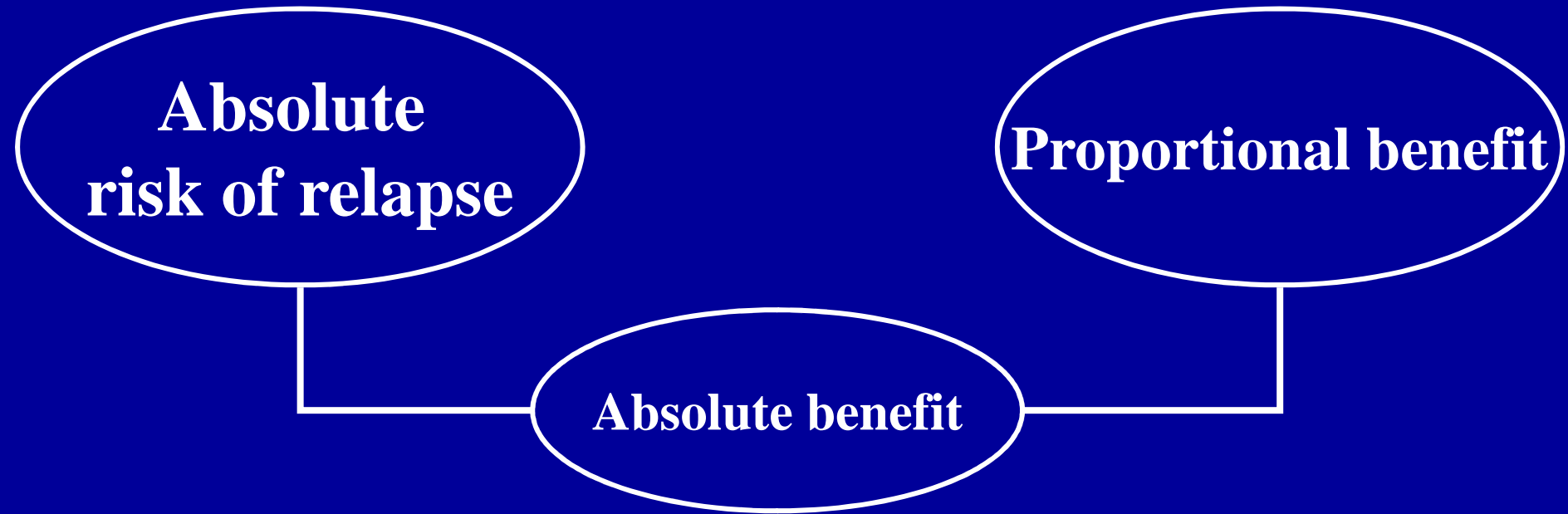


Smith I et al, Lancet 2007; 369: 29-36; Slamon D et al, Cancer Res 2009, 69:24s, abstr 62; Perez EA et al, J Clin Oncol 2007, 25:18s, abstr 512

# Summary

- **pT1pN0 (and more specifically pT1a – pT1b pN0) tumors have an increased probability of relapse if HER-2 + or triple negative (less evidence for the latter subgroup). 5 yr. absolute risk of distant relapse for pT1a – b pN0 HER-2 + patients =  $\pm 10 - 15\%$**
- **Proportional benefits from adjuvant systemic therapies are independent of disease stage (i.e. nodal status and tumor size)**

# Absolute benefits vs. treatment-related side-effects



↑ Risk of Relapse and ↑ Proportional Benefit → ↑ Absolute benefit



Absolute benefit

Side-effects (long-term)

# Known long-term side-effects from adjuvant chemotherapy: Anthracyclines (pt. I)

## Congestive heart failure

	<u>NCI - Milan</u>	<u>NCI - Canada</u>	<u>FASG - France</u>
<b>Regimen</b> (planned cumulative dose, mg/m <sup>2</sup> )	A-CMF (300)	CEF (720)	FEC 100 (600)
<b>Median follow-up, yrs.</b>	14	10	10
<b>% CHF, no. pts.</b>	1%, 6/637	1.1%, 4/351	1.1%, 3/276

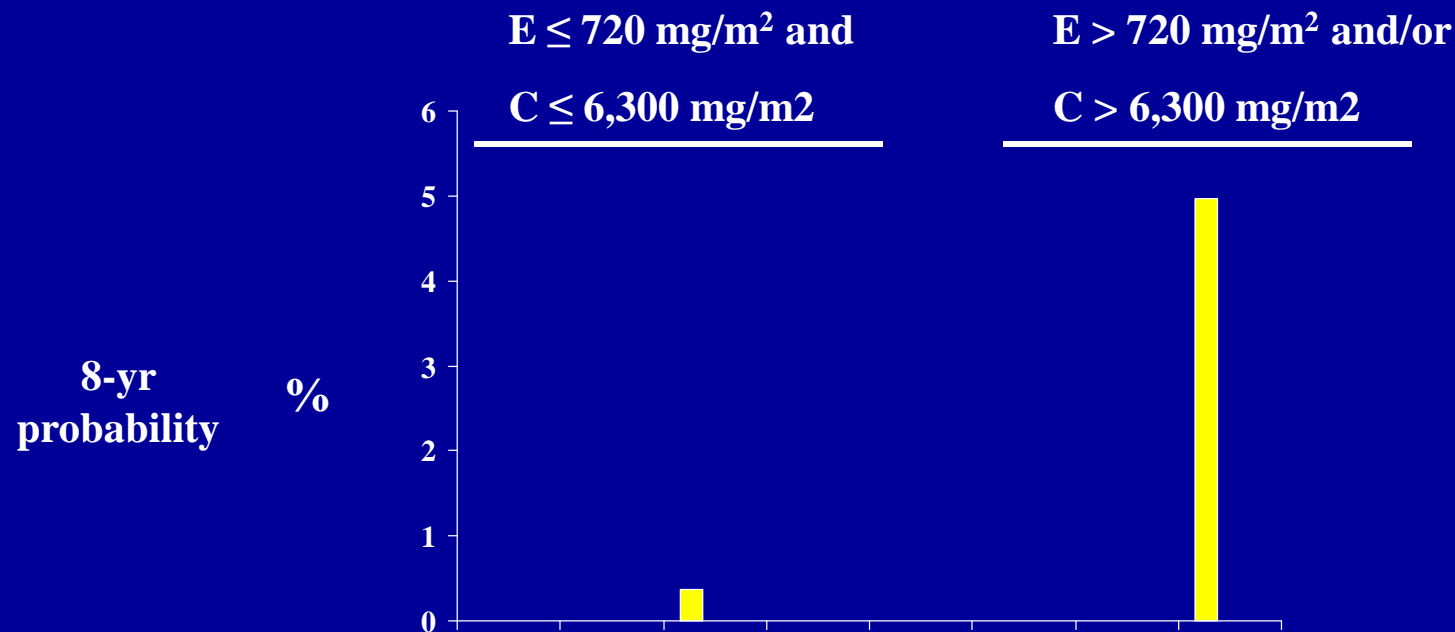
The clinical relevance of systolic dysfunction detected instrumentally years after the end of adjuvant chemotherapy is uncertain (incidence ranging from 3.1 to 5.9%)

# Known long-term side-effects from adjuvant chemotherapy: Anthracyclines (pt. II)

Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS)

- 19 randomised trials of epirubicin-based adjuvant treatment (N= 7,110 patients)
- 8-year cumulative probability of AML/MDS = 0.55% (95% CI : 0.33 – 0.78%)

Probability by administered doses of Epirubicin (E) and Cyclophosphamide (C)



## Cardiac events in patients treated with adjuvant trastuzumab in the context of phase III trials

Study	No. pts	Cardiac event rate %	Recovery rate %	Cardiac death %
<b>• B-31 + N9831</b>				
- AC → P	1,775	0.5	43	0.11
- AC → P + H → H	1,799	2.0	86	0.17
<b>• HERA</b>				
- Anthra-based	1,698	0.7	-	0.1
- Anthra-based → H	1,703	4.3	81	0
<b>• FinHER</b>				
- D → Anthra-based	116	1.7	-	0
- D + H → Anthra-based	116	0.9	-	0
<b>• BCIRG 006</b>				
-AC → D	1,073	0.7	-	0
-AC → D + H → H	1,074	2.0	-	0
-TCH → H	1,075	0.4	-	0

# Summary

- **Incidence of long-term side effects by adjuvant anthracyclines or trastuzumab does not seem to outweigh benefits deriving from these treatments**
- **Considering the fact that absolute benefits from adjuvant therapies will be smaller in pT1pN0 than in more advanced stage tumors, adjuvant treatments with the smallest risk of long-term side-effects should be prioritized**

# Potential options for adjuvant treatment of endocrine-resistant pT1a-b pN0 tumors

## HER-2 +

- Docetaxel-Cyclophosphamide (TC) x 4 + trastuzumab\* → trastuzumab (lack of phase III data)
- Docetaxel-Carboplatin-Trastuzumab (TCH) x 6 → trastuzumab (BCIRG 006 data)

## Triple negative

- Docetaxel-Cyclophosphamide (TC) x4
- CMF x 6 (no alopecia)

lack of prospective data from phase III trials

\* concomitant trastuzumab > sequential trastuzumab (?)

# Options still experimental for daily practice

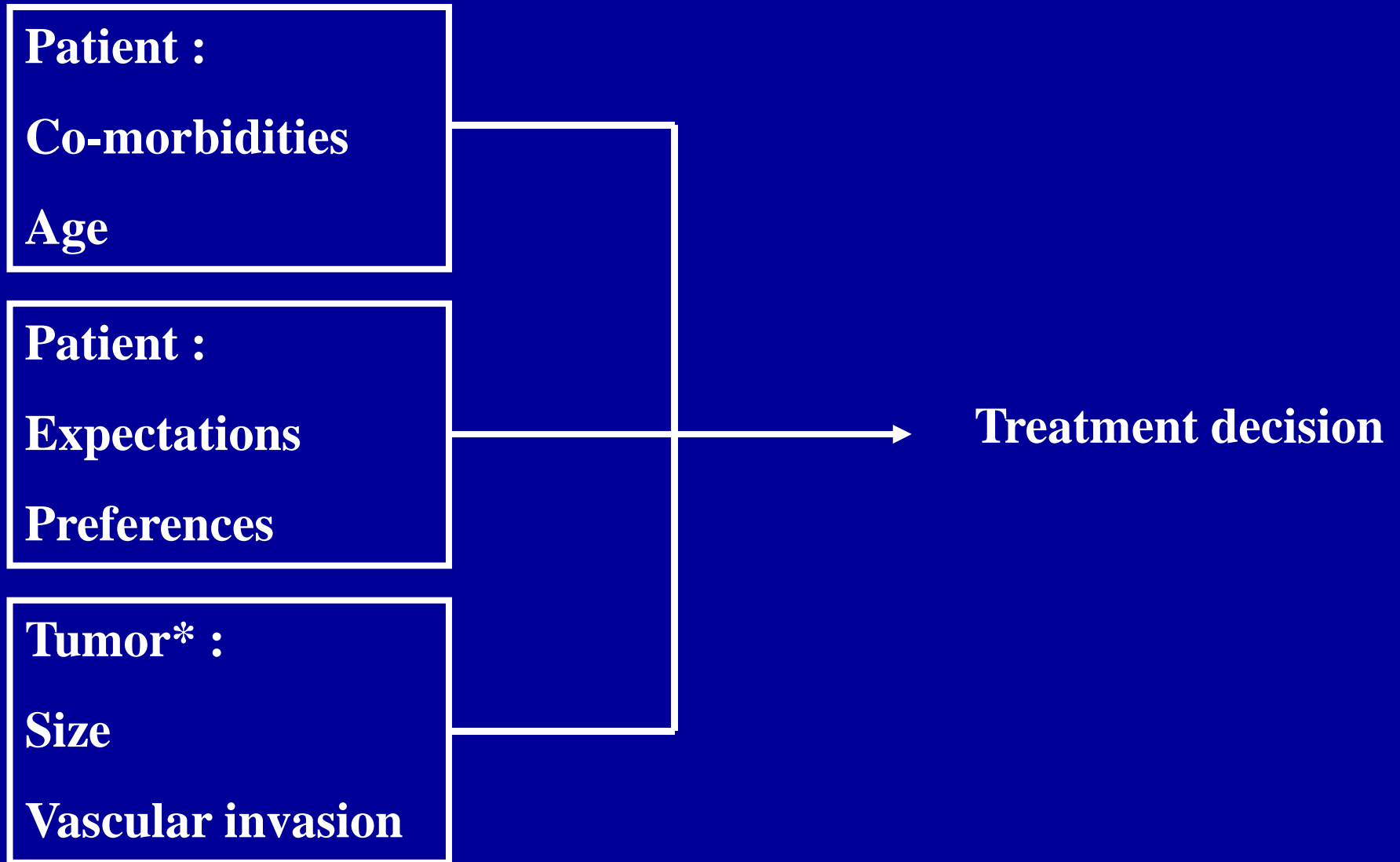
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- **Less than 1 year trastuzumab treatment (i.e. FinHER schedule)**

**Ongoing trials are assessing the efficacy of shorter trastuzumab-based treatments (Phare, ShortHER, SOLD)**

- **Trastuzumab either alone or in combination with hormonotherapy (and without chemotherapy)**

# Treatment decision: a multi-factorial process



\* pT ≤ 2cm, pN0, HER-2 + or triple negative ductal infiltrating carcinoma