

**Do you believe that dual HER2 blockade combined with chemotherapy is the best strategy for neoadjuvant therapy in a patient with operable HER2-positive breast cancer?**

**1. Yes**

**2. No**

**3. Uncertain**

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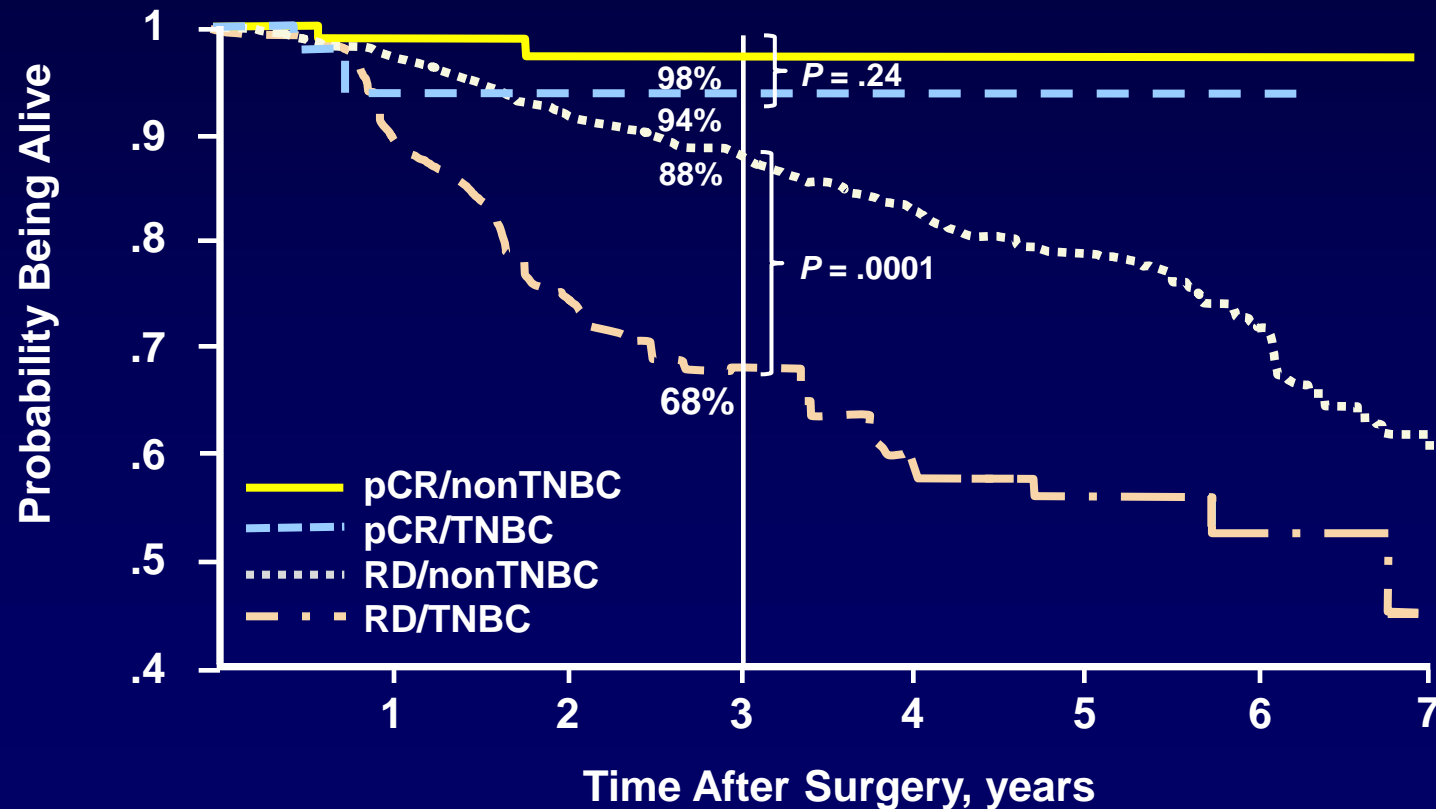
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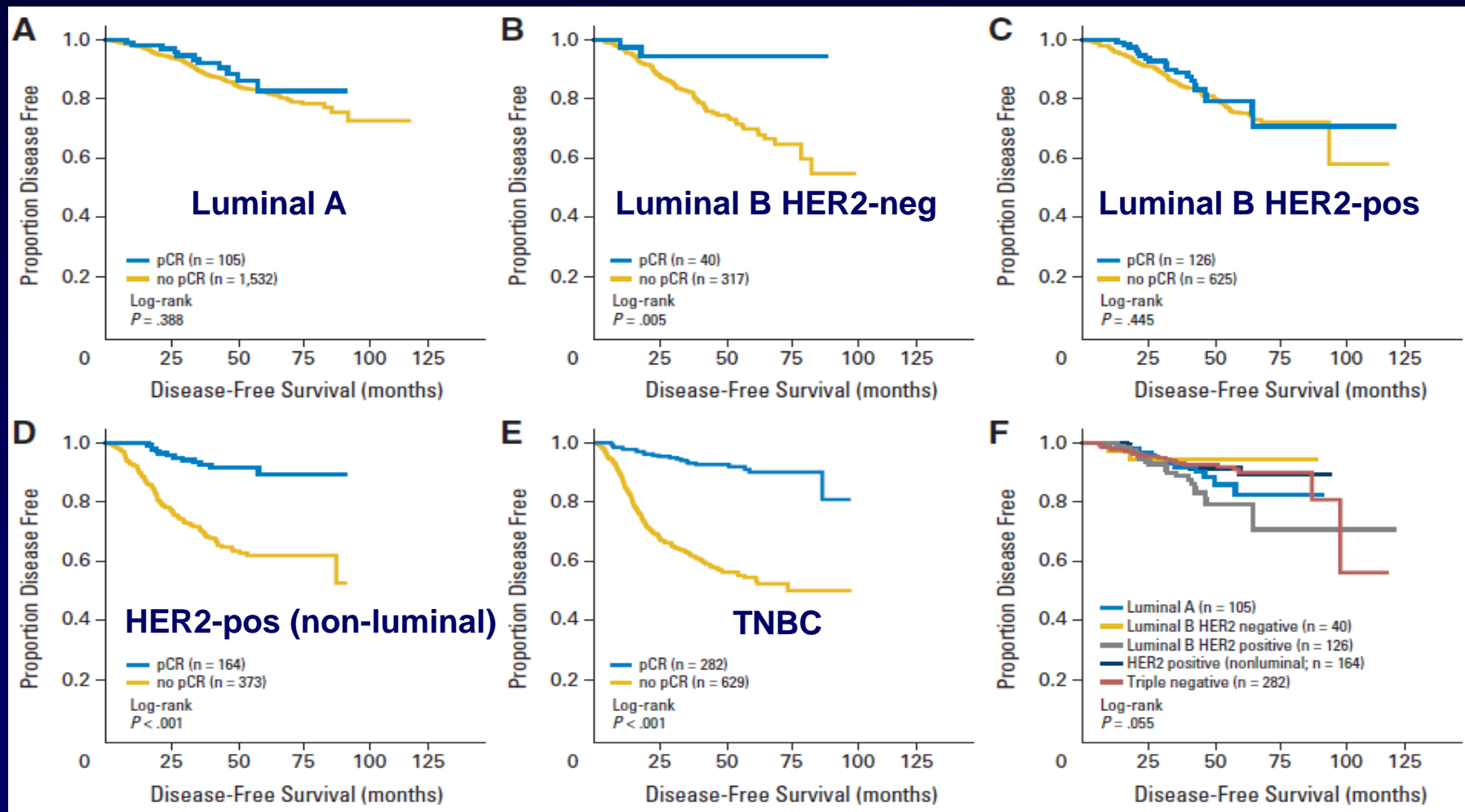
# **Question #4: Role of Combining Anti-HER Therapies in the Neoadjuvant Setting for HER2-Positive Early Breast Cancer**

**Javier Cortés, MD, PhD**  
Vall d'Hebron University Hospital  
Barcelona, Spain

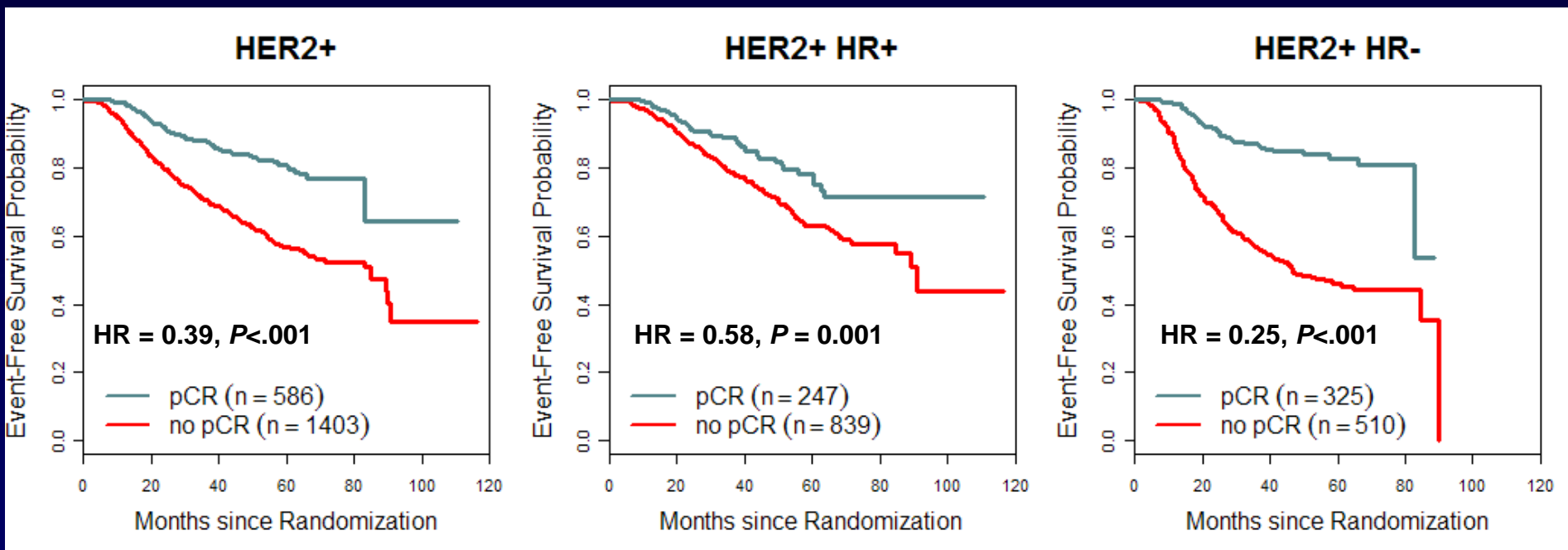
# Response to Neoadjuvant Chemotherapy and Overall Survival (OS) in Triple Negative Breast Cancer (TNBC) and Non-TNBC



# pCR and Prognosis by Subtype (N = 4193)



# Association of pCR With EFS in HER2+ Subtype



pCR = ypT0/is ypN0

# **Guidance for Industry**

## **Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval**

*Additional copies are available from:*

*Office of Communications, Division of Drug Information  
Center for Drug Evaluation and Research*

*Food and Drug Administration  
10903 New Hampshire Ave., Bldg. 51, rm. 2201  
Silver Spring, MD 20993-0002*

*Tel: 301-796-3400; Fax: 301-847-8714; E-mail: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**May 2012  
Clinical/Medical**

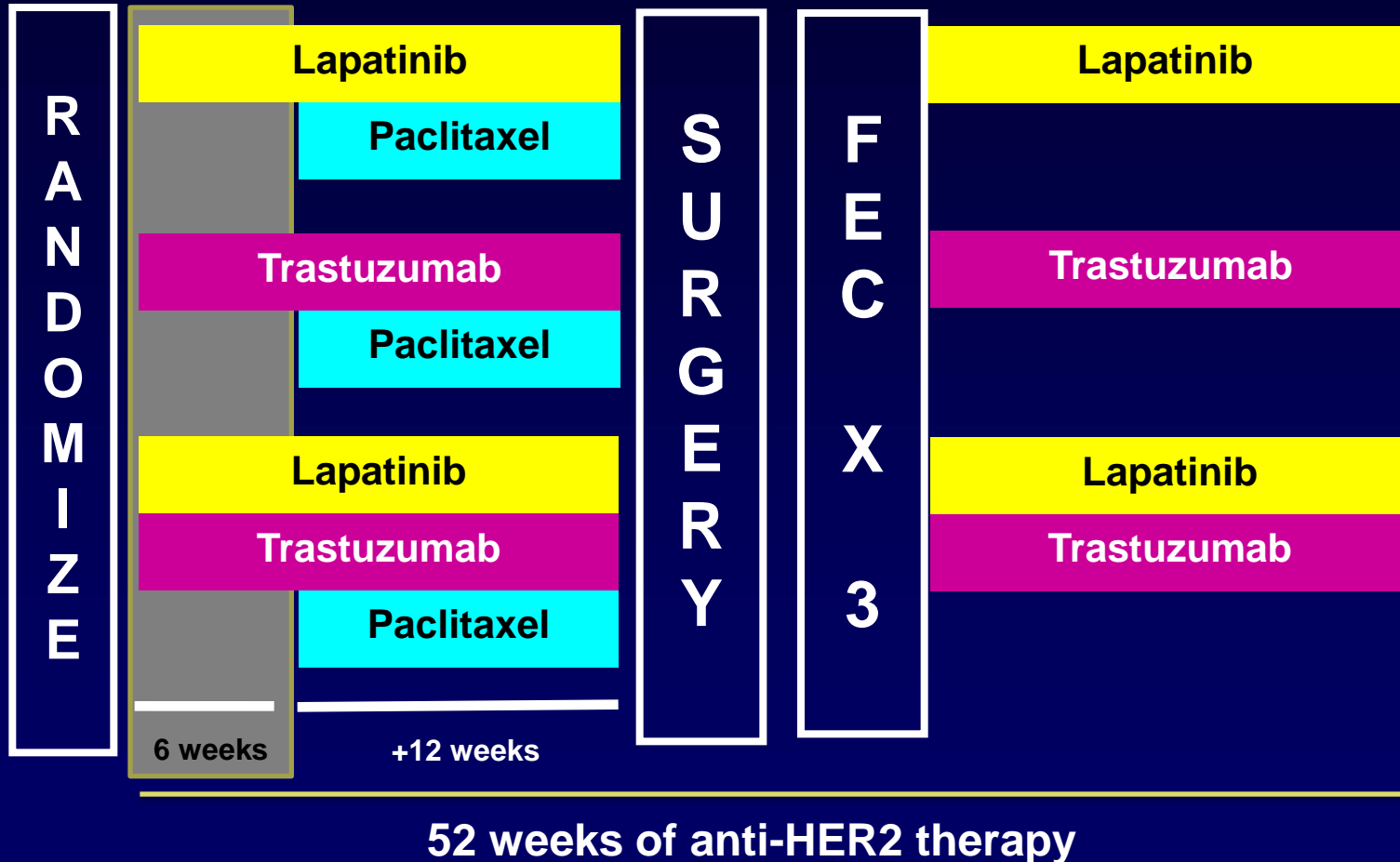
# NeoALTTO Study Design

## Eligibility

- Invasive operable HER2+ breast cancer
- Tumor >2 cm (inflammatory breast cancer excluded)
- LVEF  $\geq 50\%$

## Stratification

- Tumor  $\leq 5$  cm vs Tumor >5 cm
- ER or PgR+ vs ER and PgR-
- N0-1 vs N $\geq 2$
- Conservative surgery or not



LVEF, left ventricular ejection fraction

Baselga J, et al. *Lancet*. 2012;379(9816):633-640.



# Study Objectives

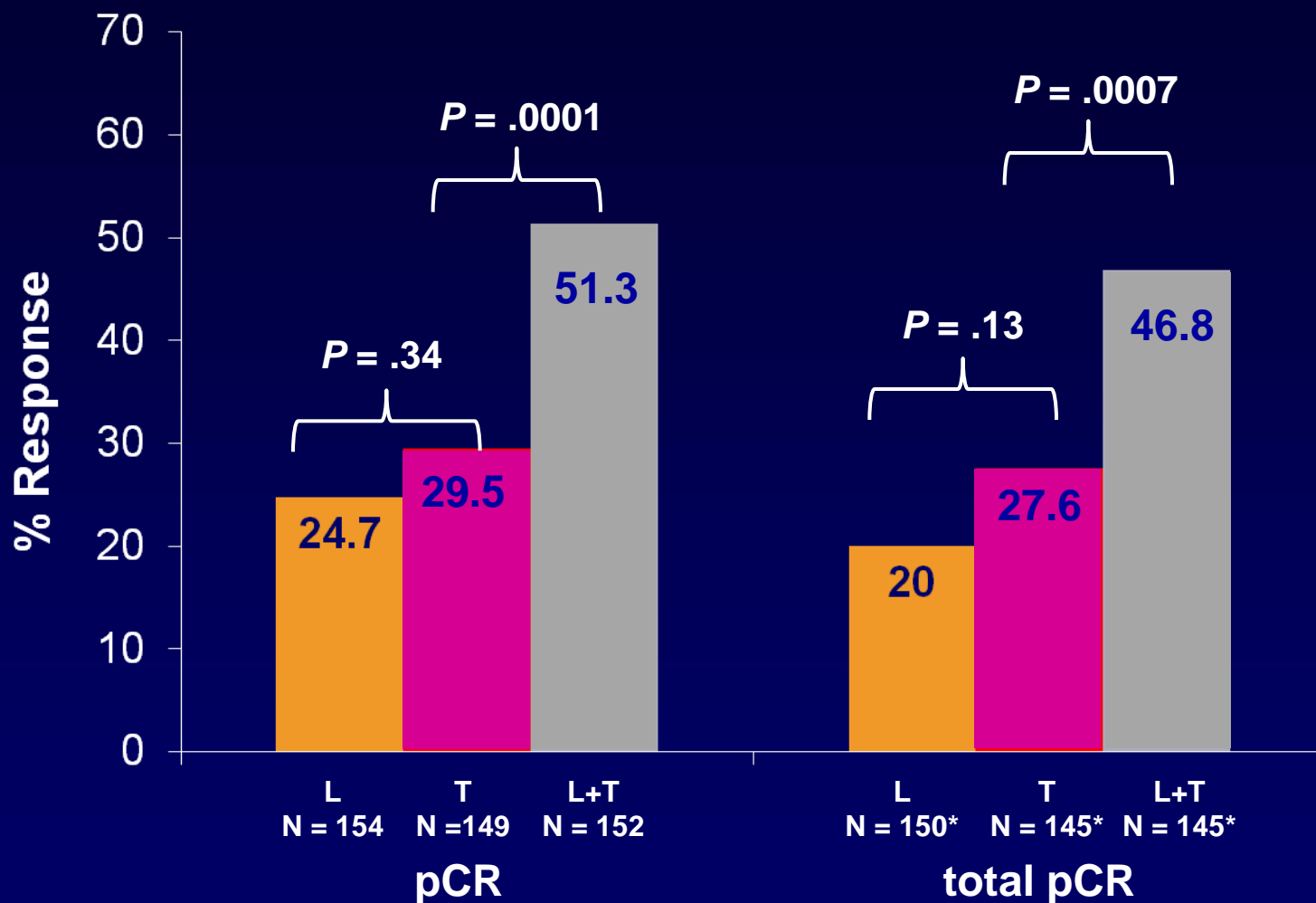
## Primary endpoint

- **pCR:** Defined according to the **National Surgical Adjuvant Breast Project guidelines** as **no invasive cancer in the breast** or only noninvasive *in situ* cancer in the breast specimen<sup>1,2</sup>

## Secondary endpoints

- pCR rate in breast AND lymph nodes [total pCR (tpCR)]
- Safety and tolerability
- Objective response rate at week 6 (end of biological window)
- Percentage of patients with node-negative disease at surgery
- Rate of conversion to breast-conserving surgery
- Rate of conversion to breast surgery in those with nonoperable disease at presentation
- Disease-free survival (DFS) and OS

# NeoALTTO: pCR and Total pCR



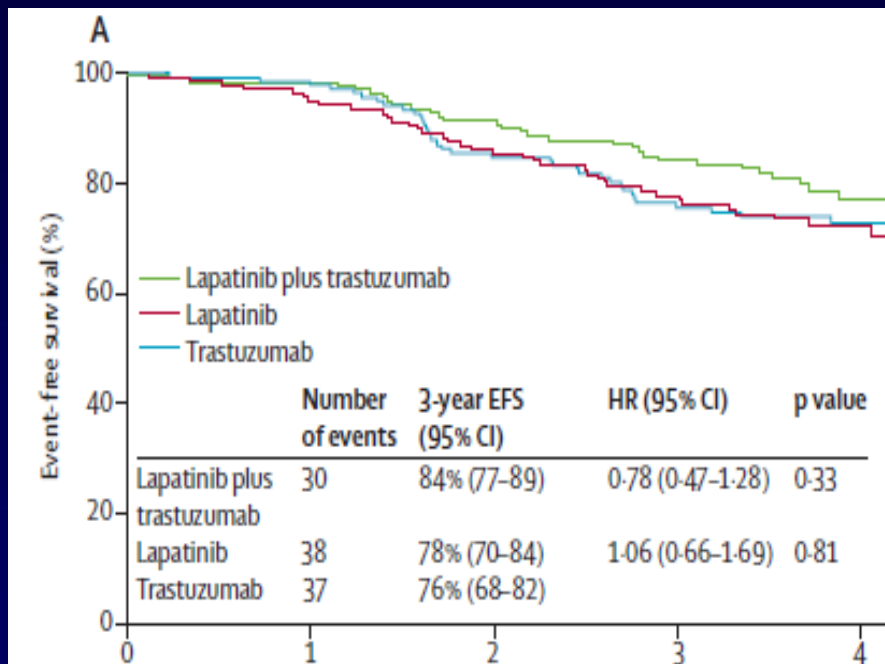
\*Excludes 15 patients with nonevaluable nodal status  
L, lapatinib; T, trastuzumab

Baselga J, et al. *Lancet*. 2012;379(9816):633-640.

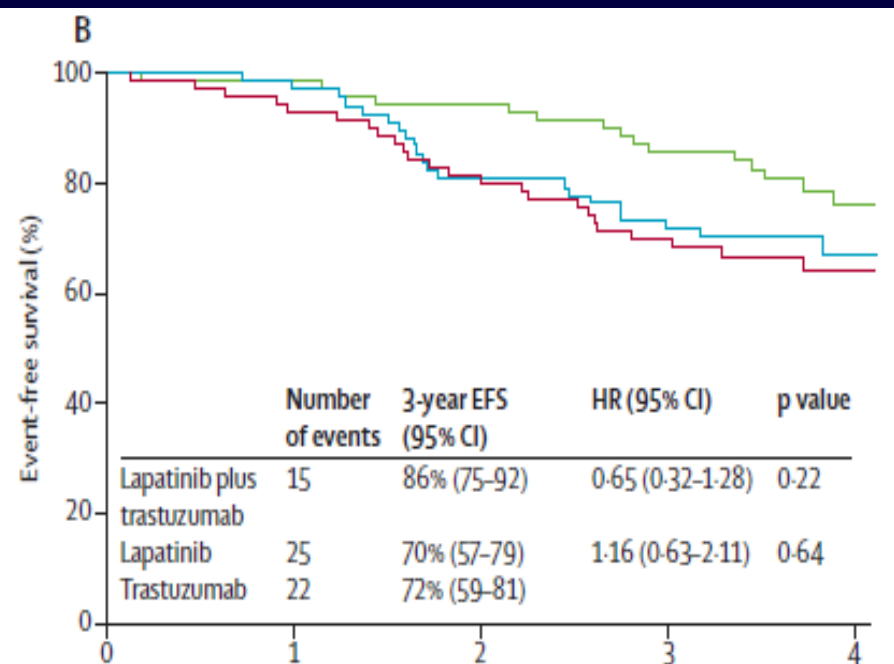
This agent may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.

# NeoALTTO: DFS

ER+



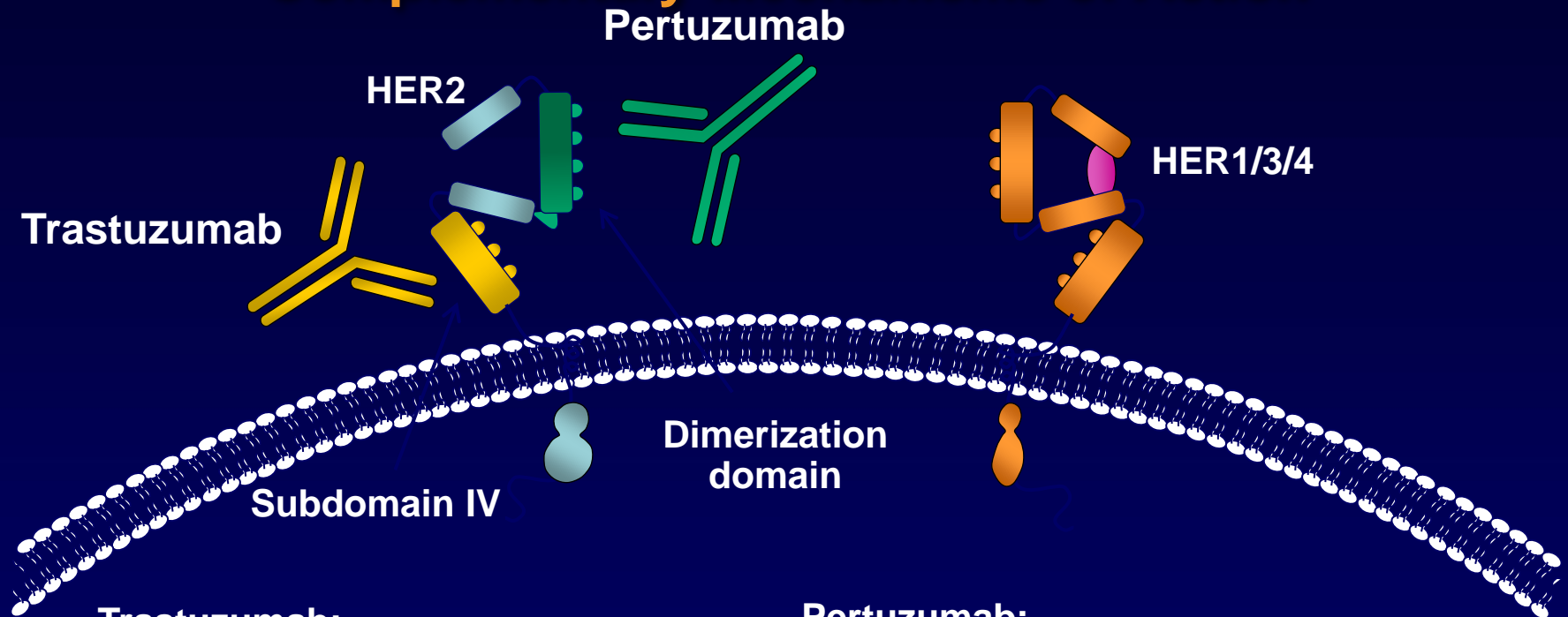
ER-



De Azambuja E, et al. *Lancet Oncol.* 2014;15(10):1137-1146.

This agent may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.

# Rationale for Combining Pertuzumab With Trastuzumab in the Clinic: Pertuzumab and Trastuzumab Have Complementary Mechanisms of Action



## Trastuzumab:

- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

## Pertuzumab:

- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

ADCC, antibody-dependent cell-mediated cytotoxicity; ECD, extracellular domain

Molina MA, et al. *Cancer Res.* 2001;61(12):4744-4749. Juntila TT, et al. *Cancer Cell.* 2009;15(5):429-440. Agus DB, et al. *Cancer Cell.* 2002;2(2):127-137. Scheuer W, et al. *Cancer Res.* 2009;69(24):9330-9336.

# NeoSphere Study Design

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

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

TH (n = 107)  
docetaxel +  
trastuzumab

THP (n = 107)  
docetaxel +  
trastuzumab +  
pertuzumab

HP (n = 107)  
trastuzumab +  
pertuzumab

TP (n = 96)  
docetaxel +  
pertuzumab

S  
U  
R  
G  
E  
R  
Y

FEC q3w x 3  
Trastuzumab q3w cycles  
5-17

FEC q3 x 3  
Trastuzumab q3w cycles  
5-17

Docetaxel q3w x 4 → FEC  
q3w x 3  
Trastuzumab q3w cycles  
5-17

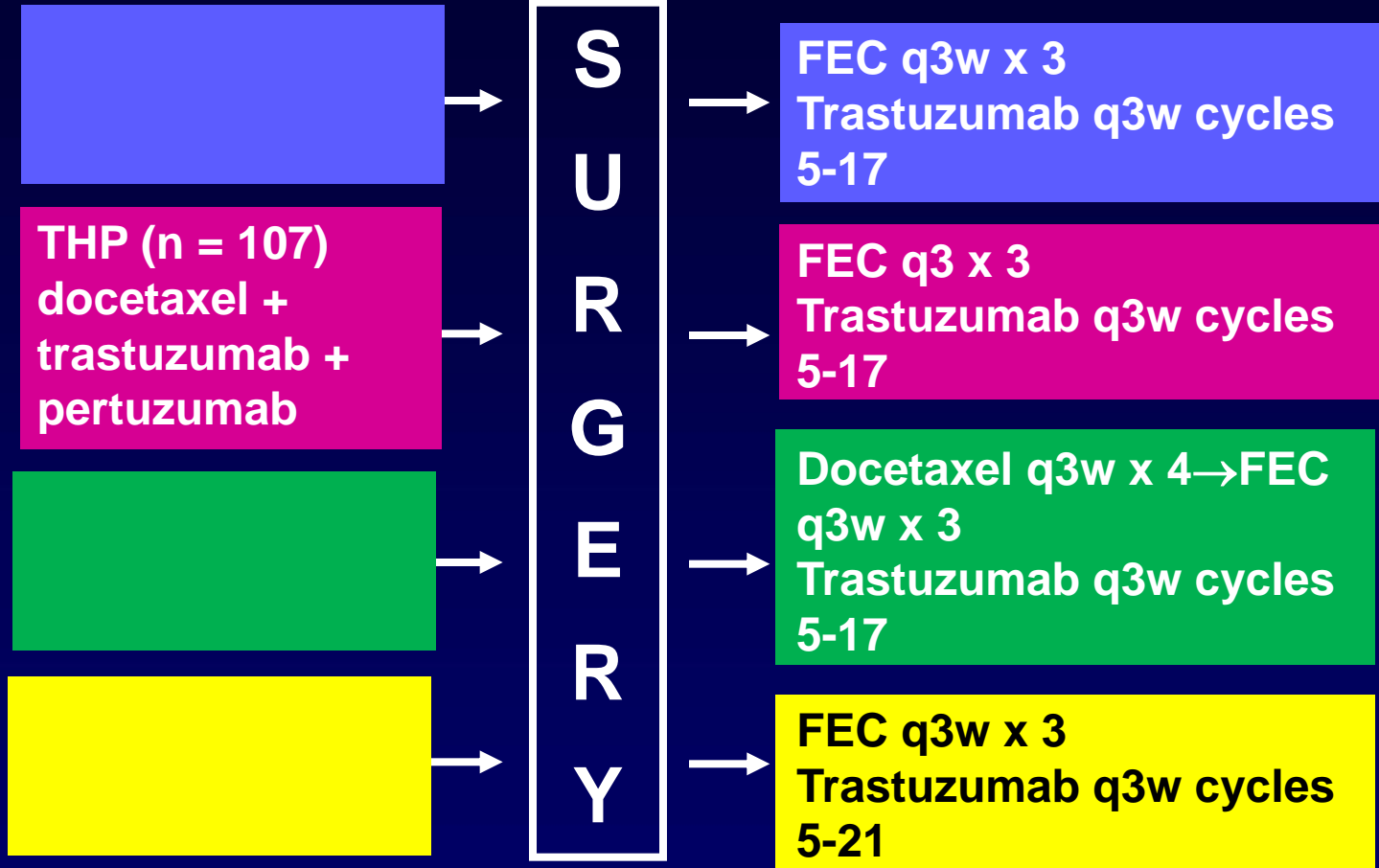
FEC q3w x 3  
Trastuzumab q3w cycles  
5-21

T, docetaxel; H, trastuzumab; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; P, pertuzumab

# NeoSphere Study Design

Patients with  
operable or  
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inflammatory  
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Chemo-naïve  
and primary  
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(N = 417)



# Study Objectives

**Primary endpoint: Comparison of pCR rates**

- TH vs THP

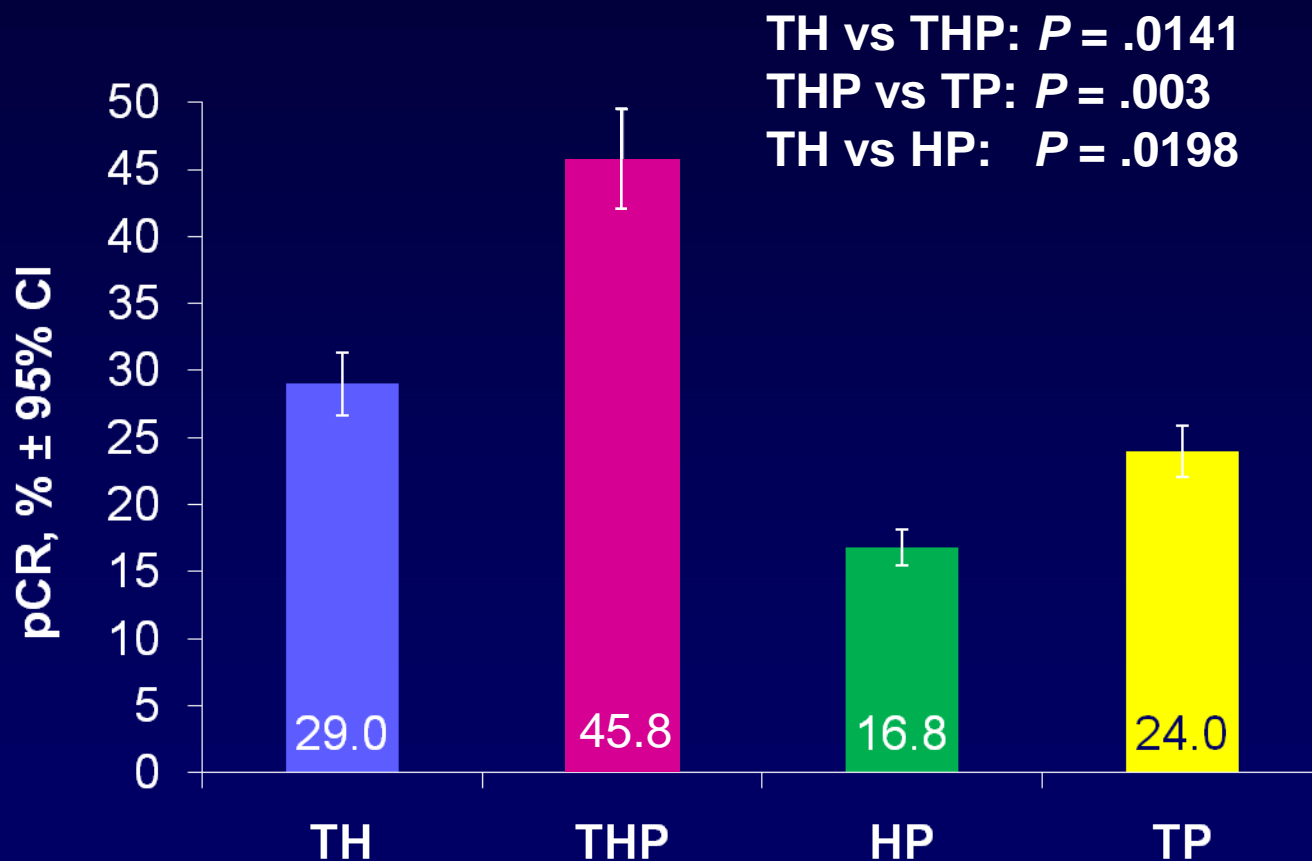
*Exploratory analyses*

- TH vs HP
- THP vs TP

**Secondary endpoints**

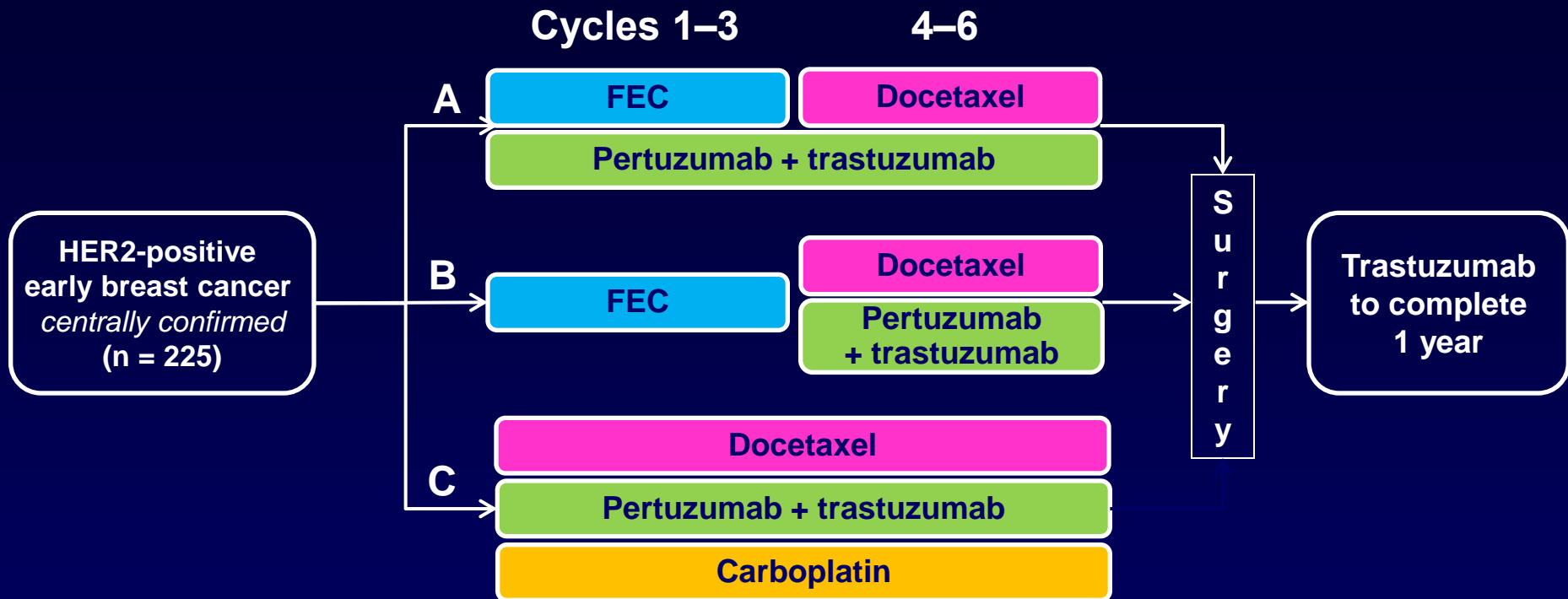
- Clinical response
- DFS
- Breast conservation rate
- Biomarker evaluation

# NeoSphere: pCR Rates (Intention-to-Treat Population)





# TRYPHAENA: Study Design



## Study dosing q3w

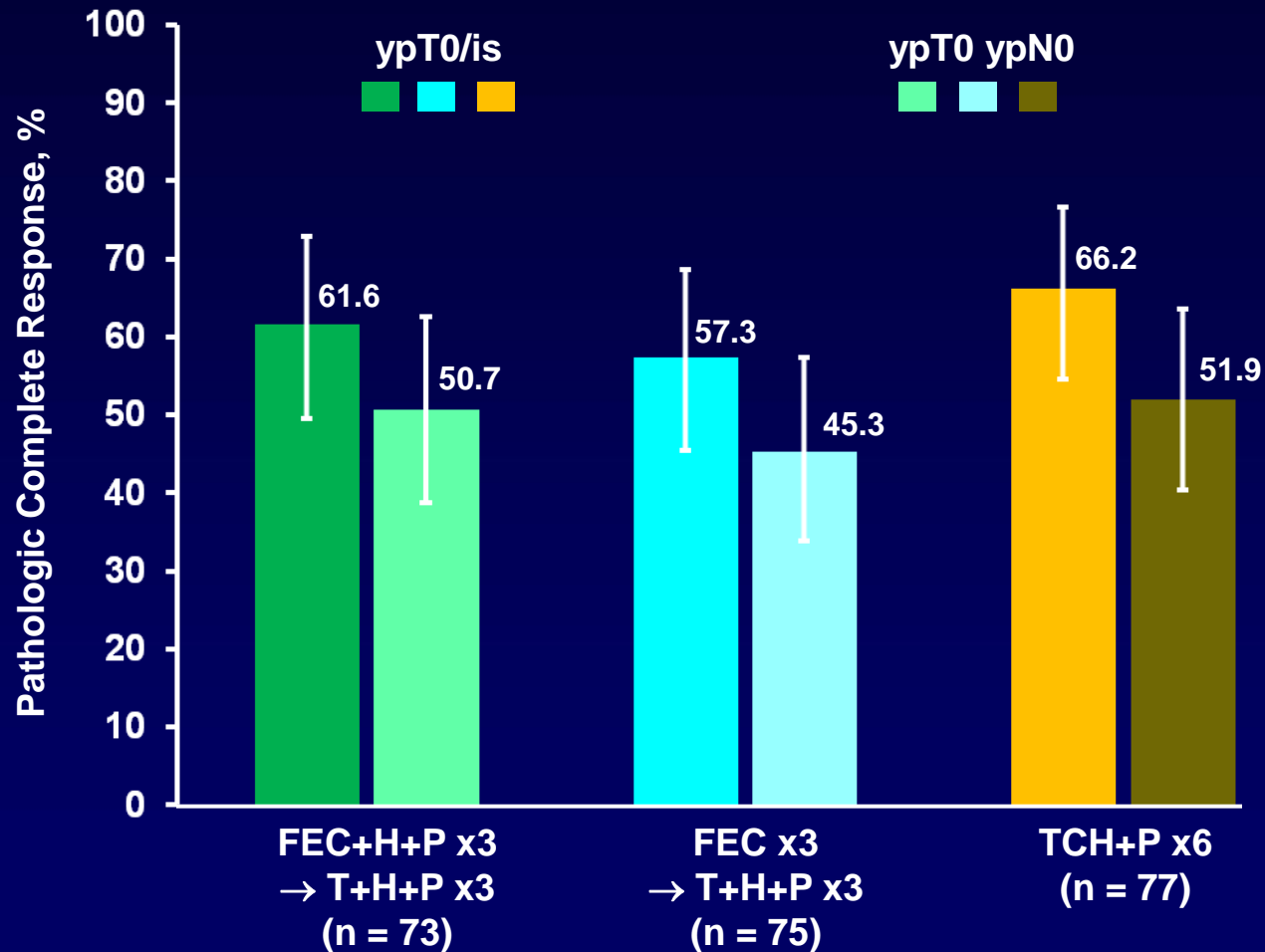
- **FEC** 500 mg/m<sup>2</sup>, 100 mg/m<sup>2</sup>, 600 mg/m<sup>2</sup>
- **Carboplatin** AUC 6
- **Trastuzumab** 8 mg/kg loading dose, 6 mg/kg maintenance
- **Pertuzumab** 840 mg loading dose, 420 mg maintenance
- **Docetaxel** 75 mg/m<sup>2</sup> (escalating to 100 mg/m<sup>2</sup> if tolerated, in arms A and B only)

AUC, area under the concentration-time curve

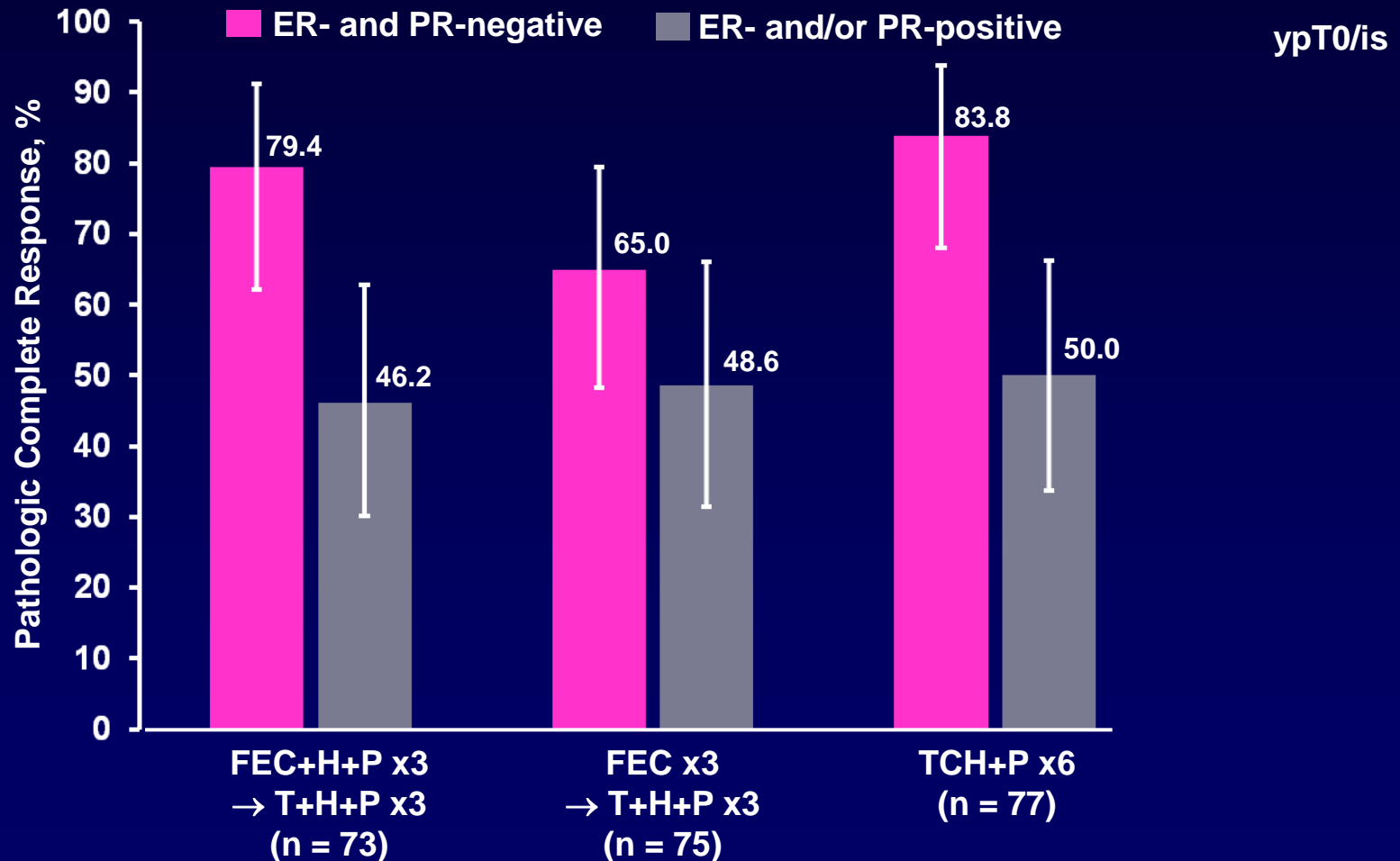
# TRYPHAENA: Cardiac Events During Neoadjuvant Treatment

	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 (%)	0 (0.0)	2 (2.7)	0 (0.0)
LVSD (all grades), n (%)	4 (5.6)	3 (4.0)	2 (2.6)
LVEF decline ≥10% points and below 50%, n (%)	3 (4.2)	4 (5.3)	3 (3.9)

# TRYPHAENA: pCR



# TRYPHAENA: pCR by Estrogen / Progesterone Receptor Status



# My Opinion

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# RAISING THE BAR IN BREAST CANCER CARE:

Answering Clinically Relevant Questions

