

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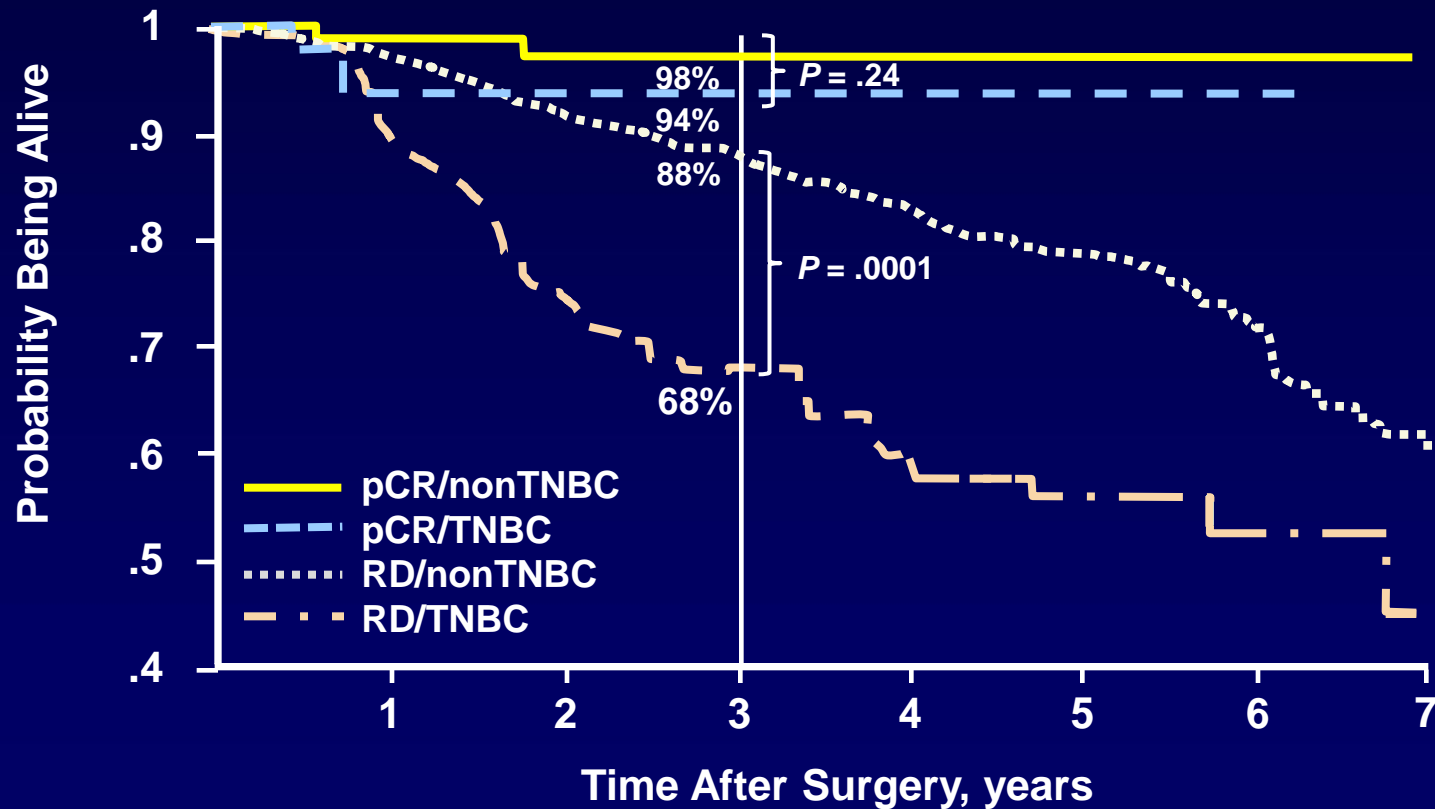
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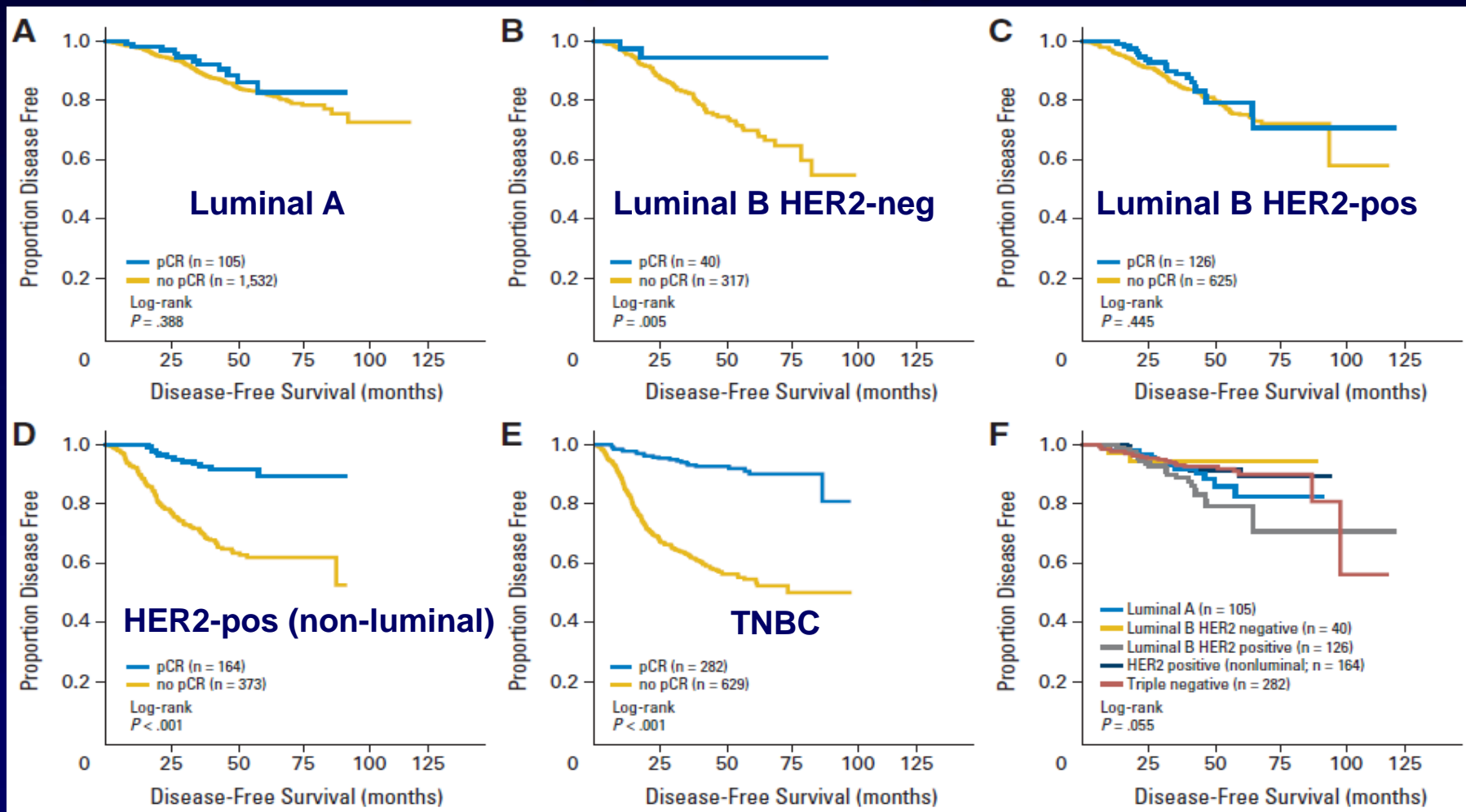
Question #4: Role of Combining Anti-HER Therapies in the Neoadjuvant Setting for HER2-Positive Early Breast Cancer

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Barcelona, Spain

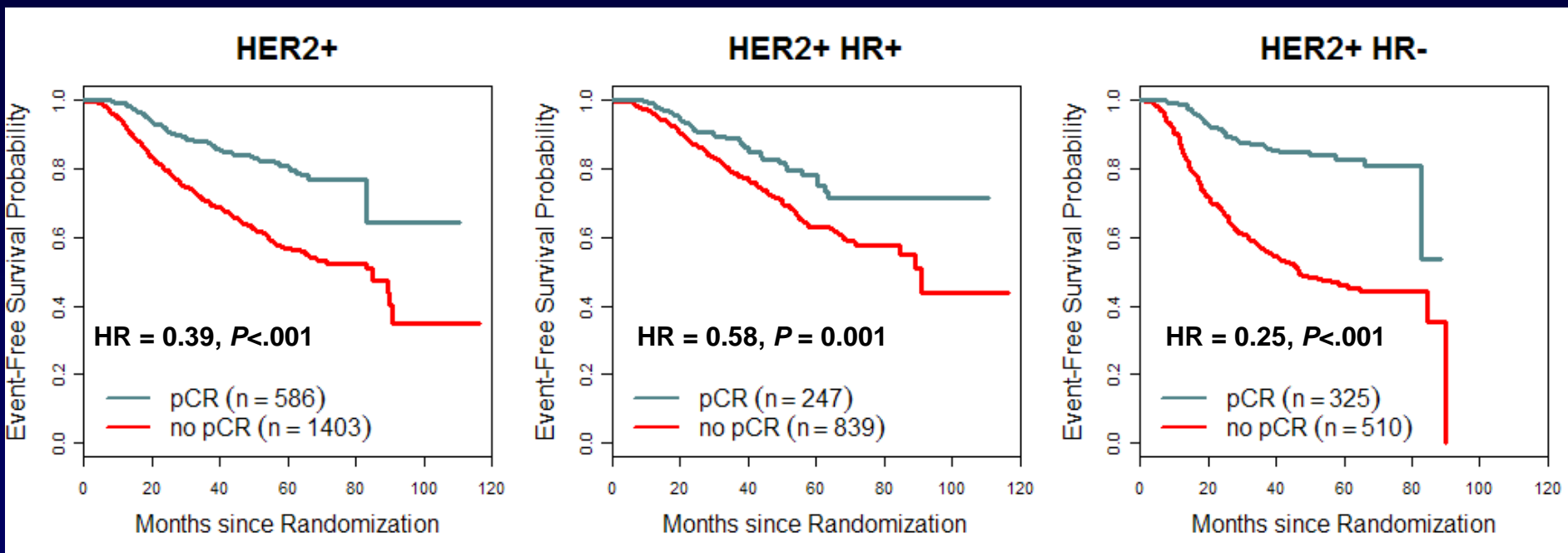
Response to Neoadjuvant Chemotherapy and Overall Survival (OS) in Triple Negative Breast Cancer (TNBC) and Non-TNBC



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
<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**

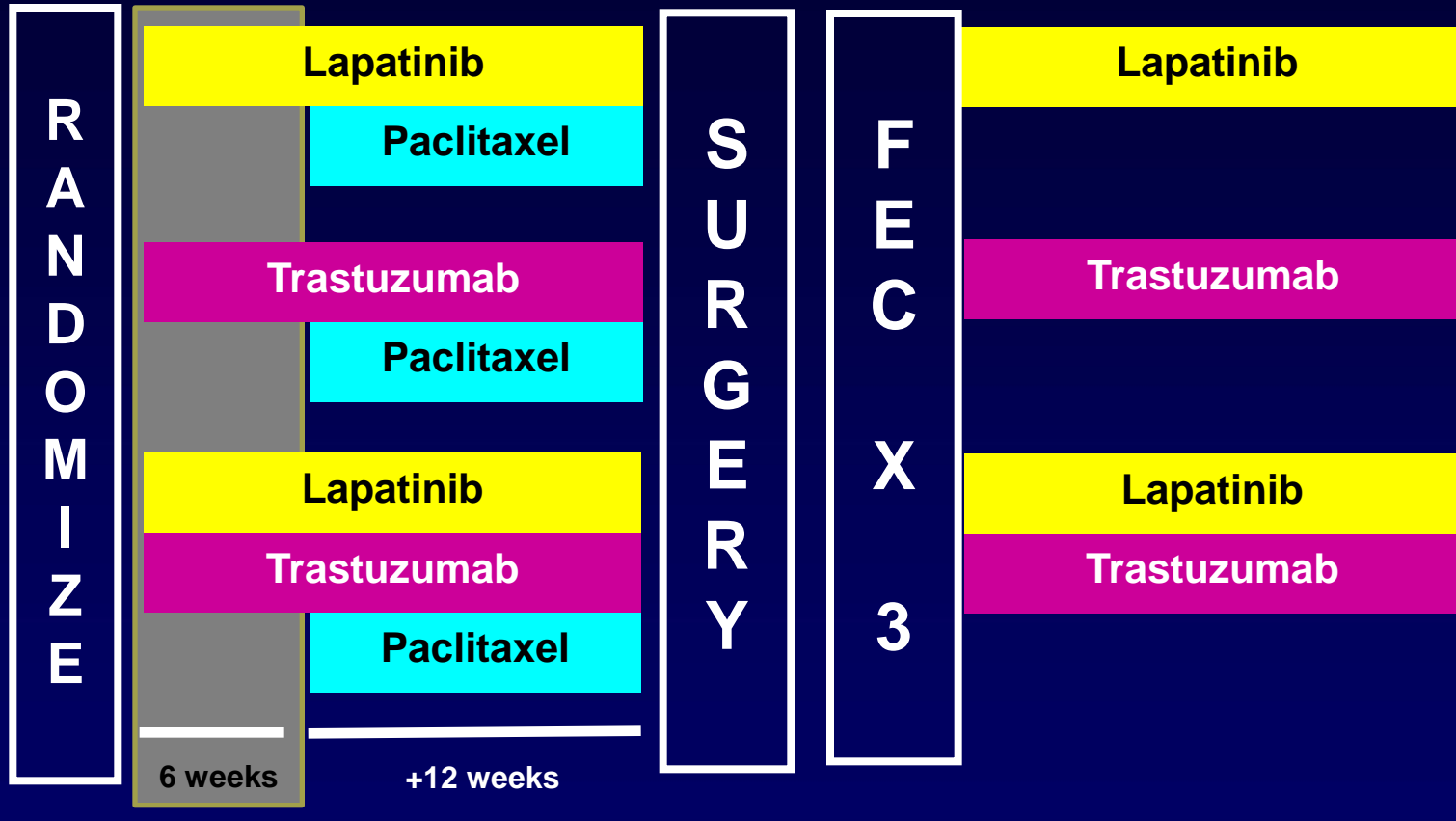
NeoALTTO Study Design

Eligibility

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

Stratification

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



52 weeks of anti-HER2 therapy

LVEF, left ventricular ejection fraction

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

Study Objectives

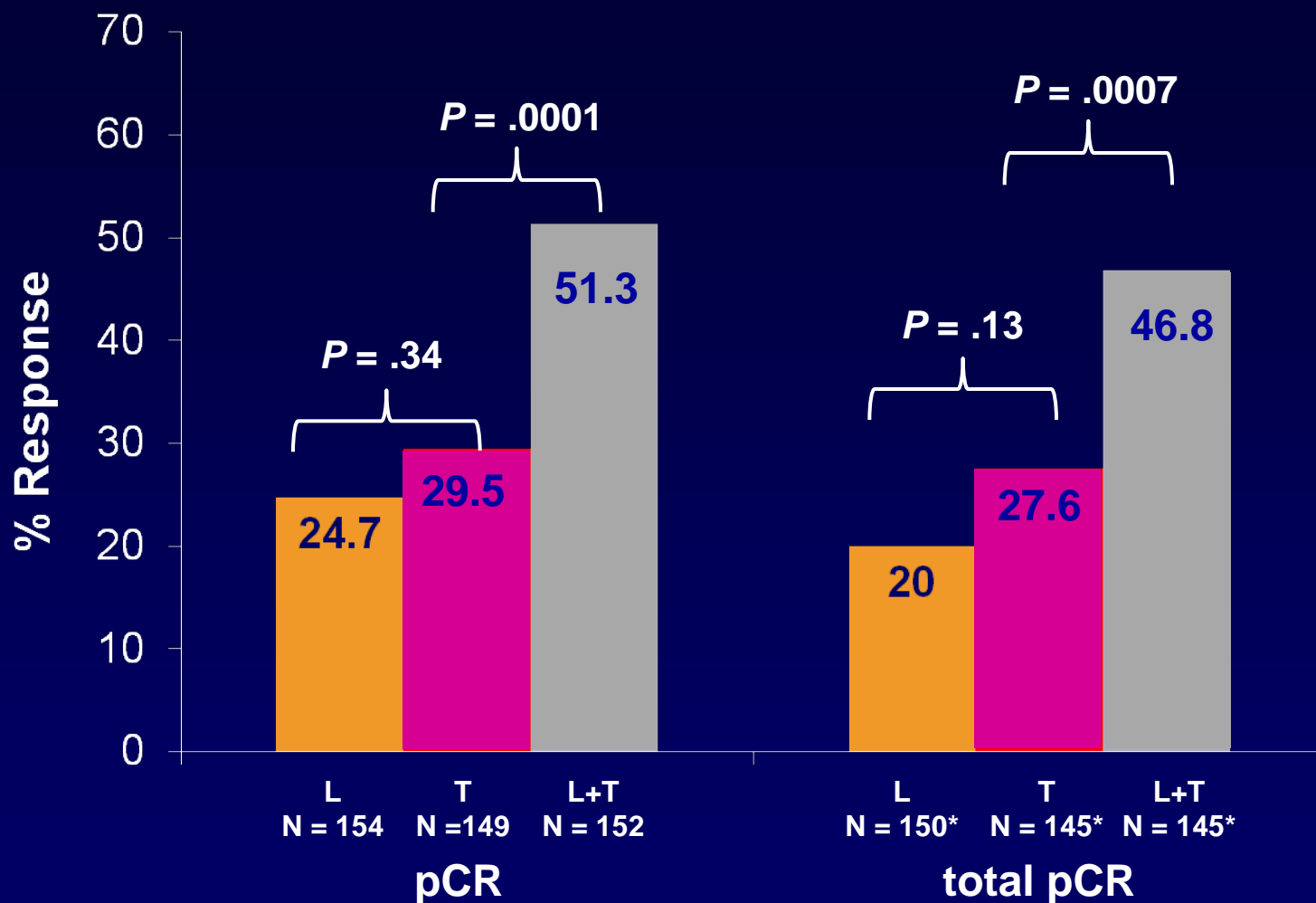
Primary endpoint

- **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^{1,2}

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



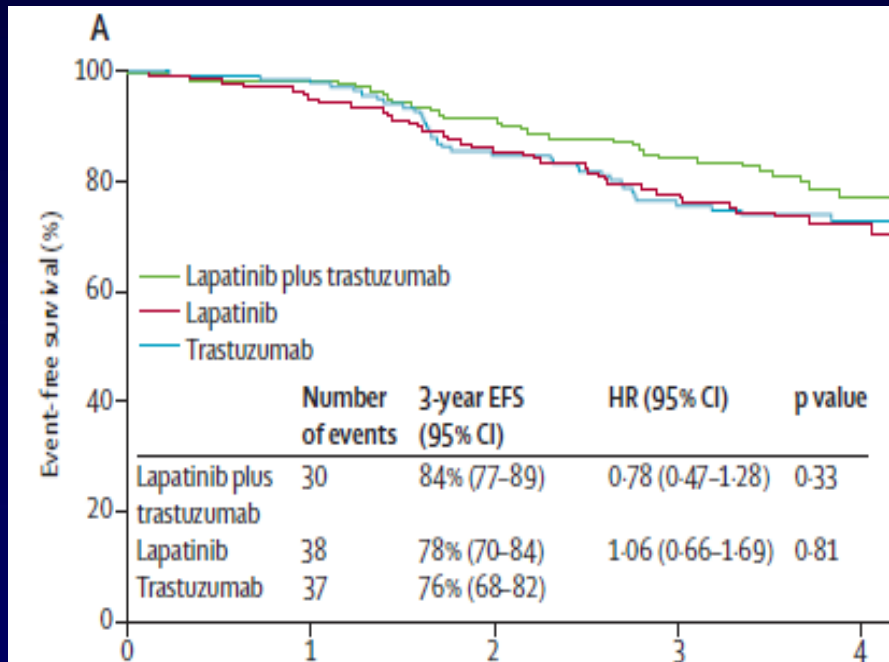
*Excludes 15 patients with nonevaluable nodal status
L, lapatinib; T, trastuzumab

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

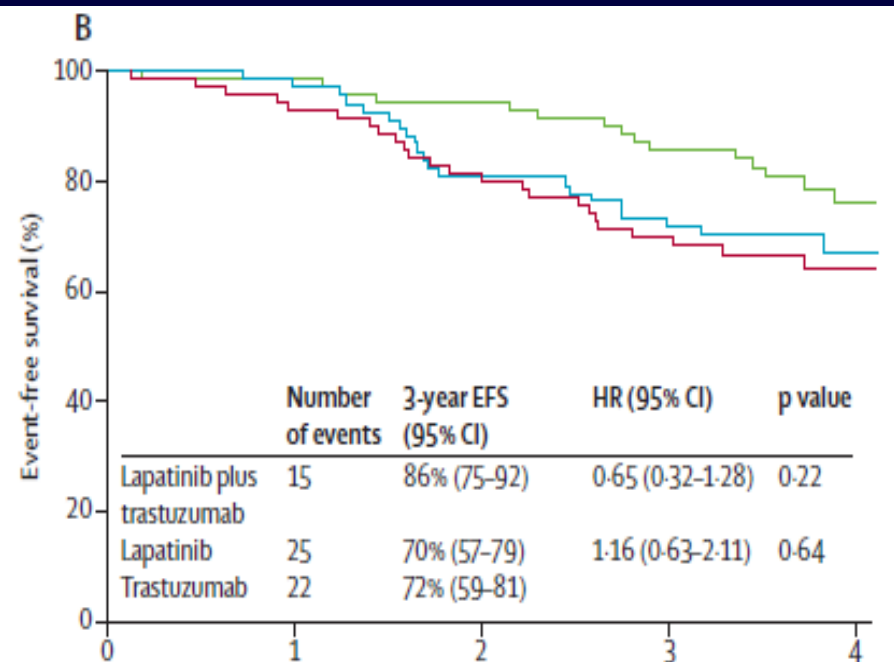
This agent may not be currently approved by the US Food and Drug Administration or European Medicines Agency for this indication.

NeoALTTO: DFS

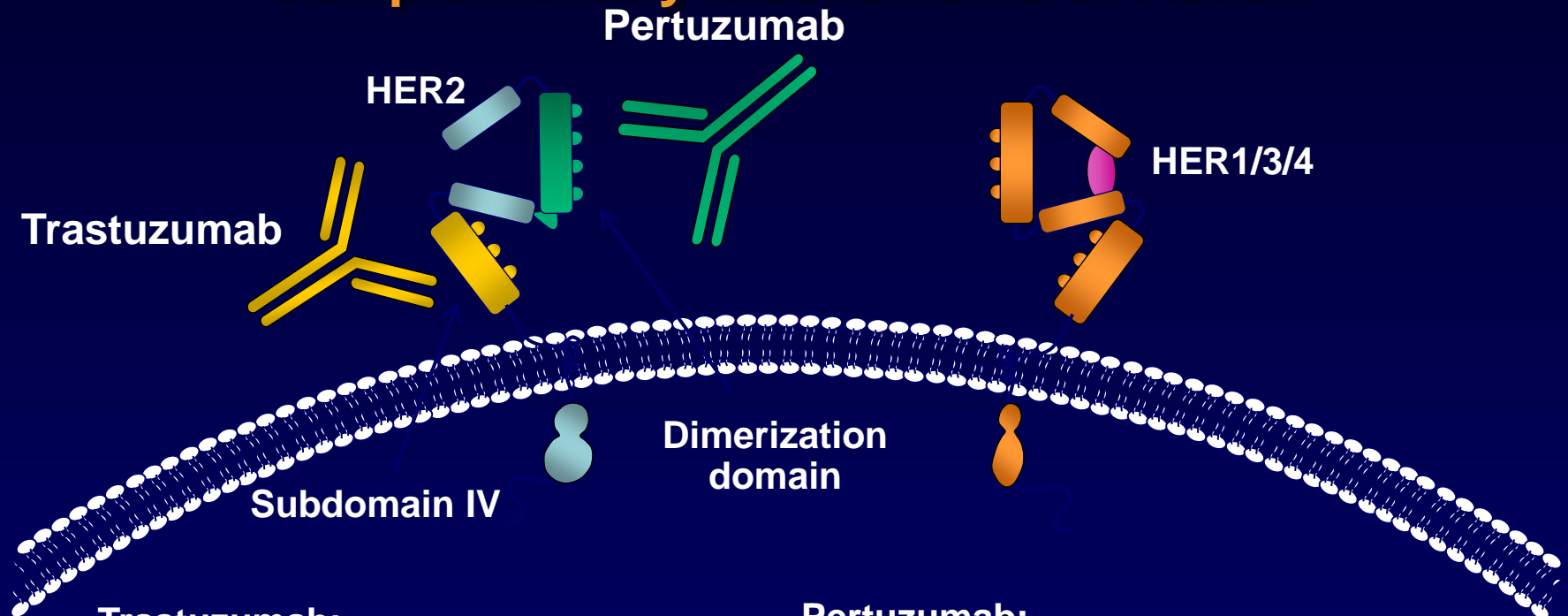
ER+



ER-



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. Junttila 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

Study Objectives

Primary endpoint: Comparison of pCR rates

- TH vs THP

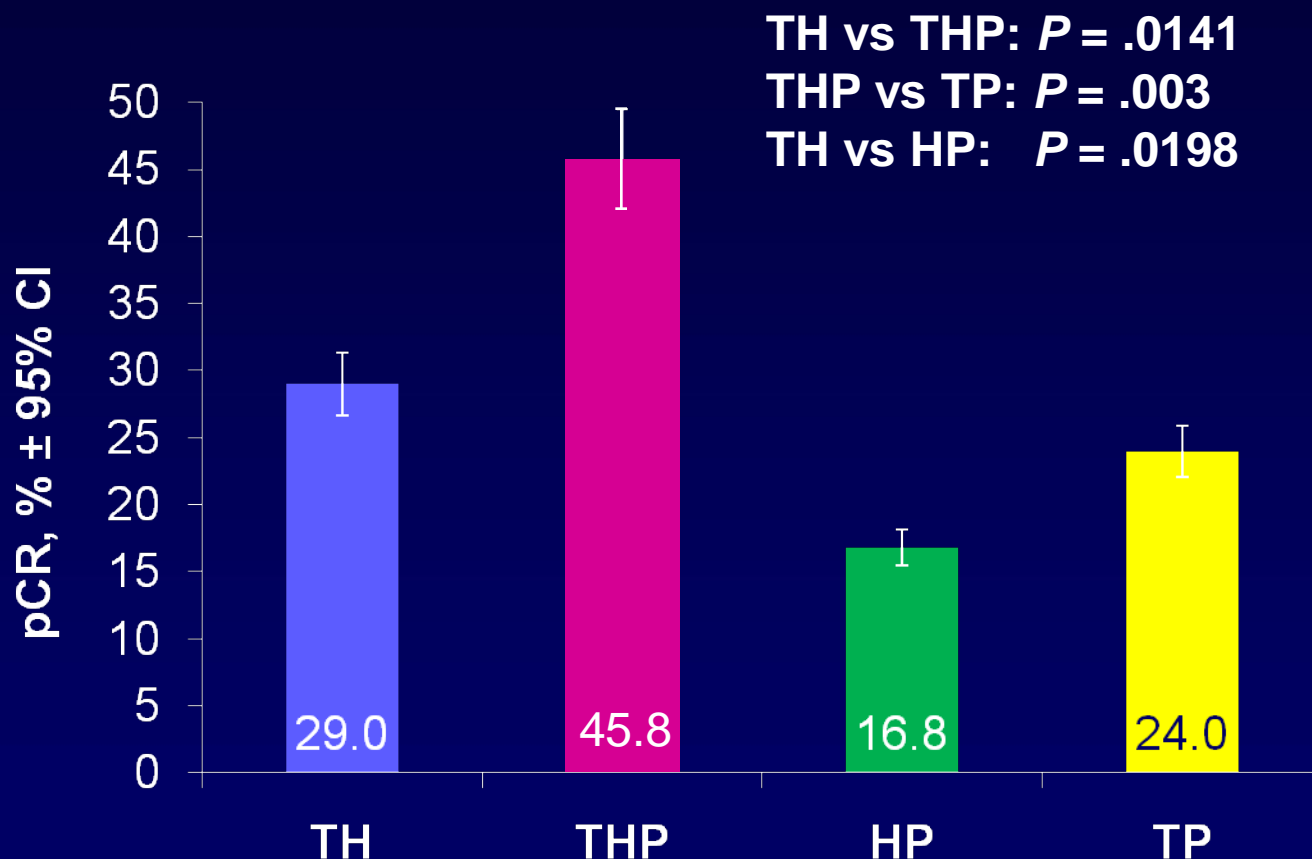
Exploratory analyses

- TH vs HP
- THP vs TP

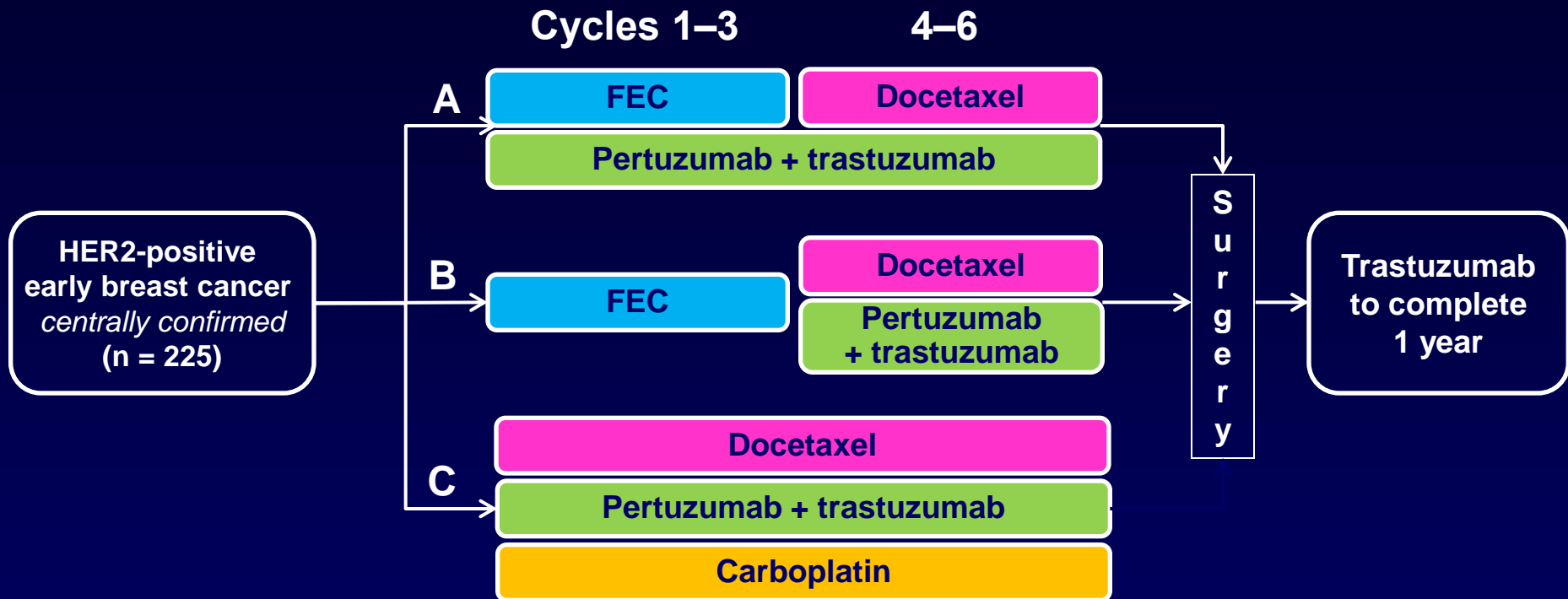
Secondary endpoints

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

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



TRYPHAENA: Study Design



Study dosing q3w

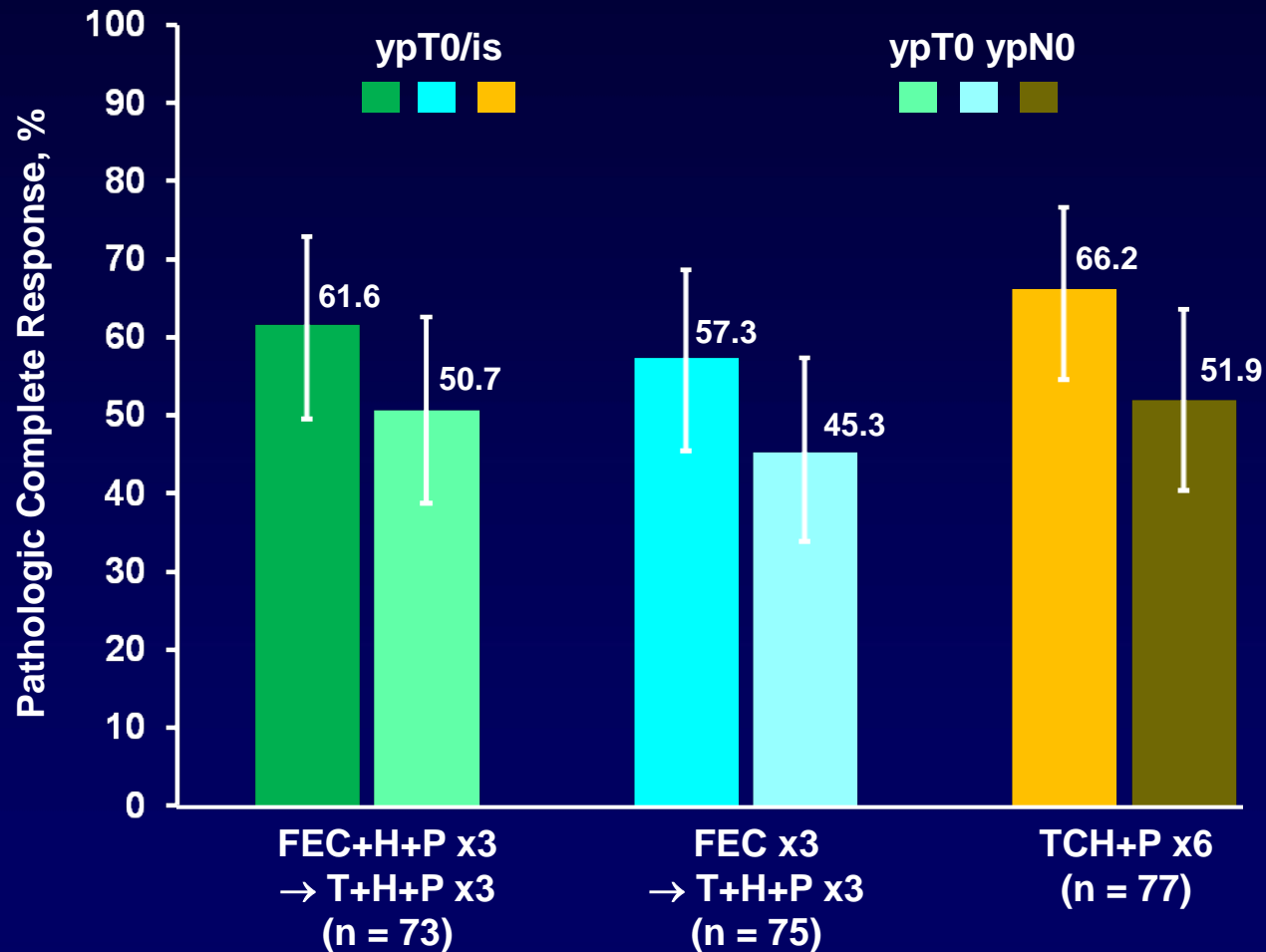
- **FEC** 500 mg/m², 100 mg/m², 600 mg/m²
- **Carboplatin** AUC 6
- **Trastuzumab** 8 mg/kg loading dose, 6 mg/kg maintenance
- **Pertuzumab** 840 mg loading dose, 420 mg maintenance
- **Docetaxel** 75 mg/m² (escalating to 100 mg/m² if tolerated, in arms A and B only)

AUC, area under the concentration-time curve

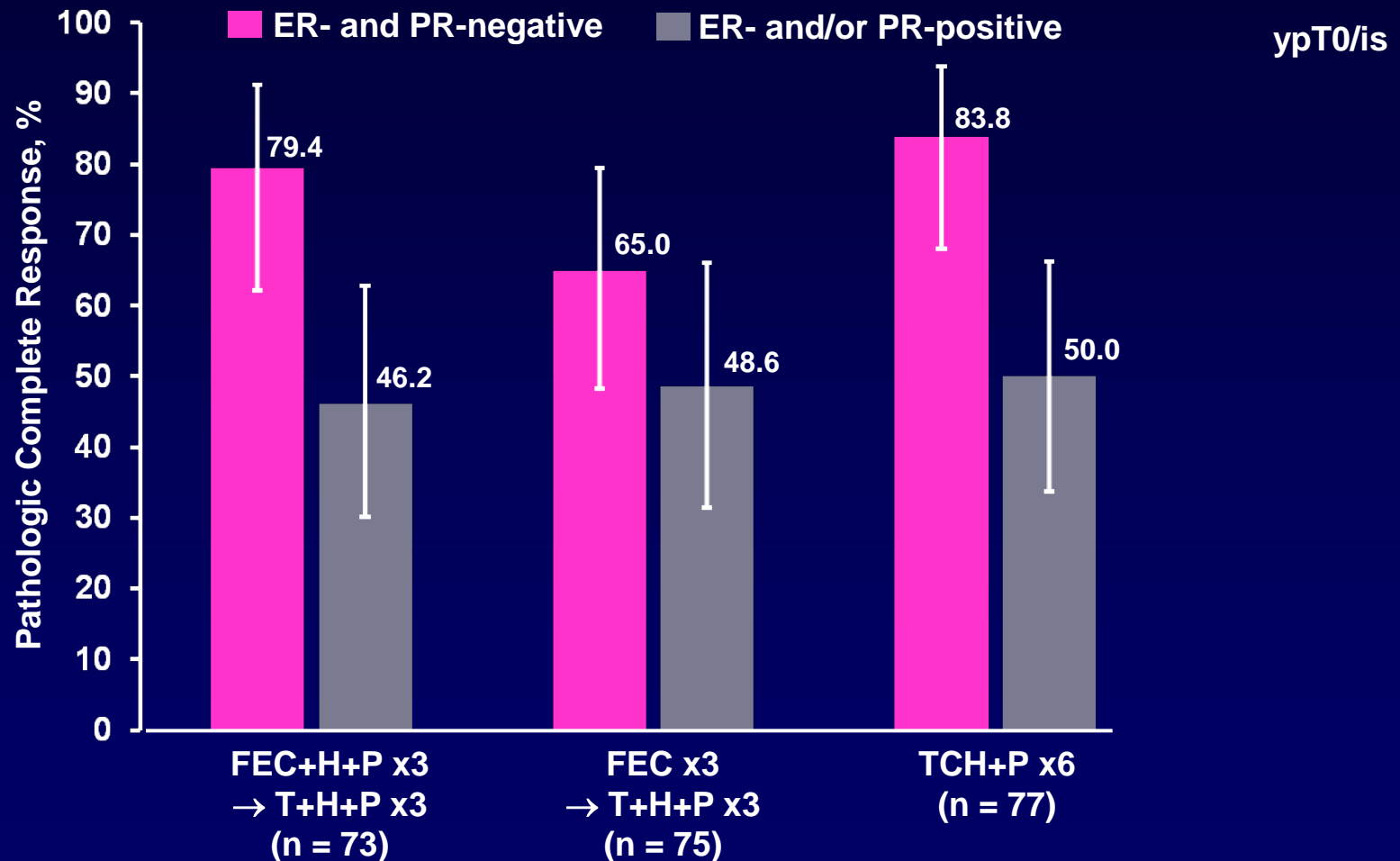
TRYPHAENA: Cardiac Events During Neoadjuvant Treatment

	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

