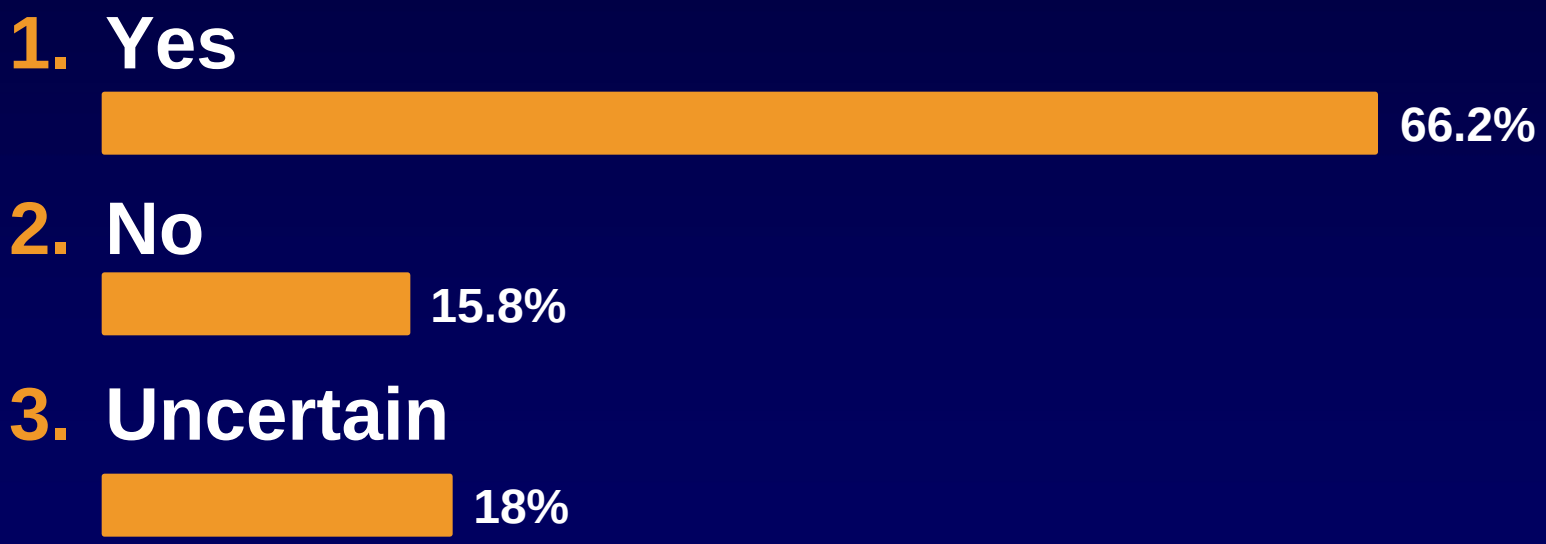
Do you believe that dual HER2 blockade combined with chemotherapy is the best strategy for neoadjuvant therapy in a patient with operable HER2-positive breast cancer?

1. Yes
2. No
3. Uncertain

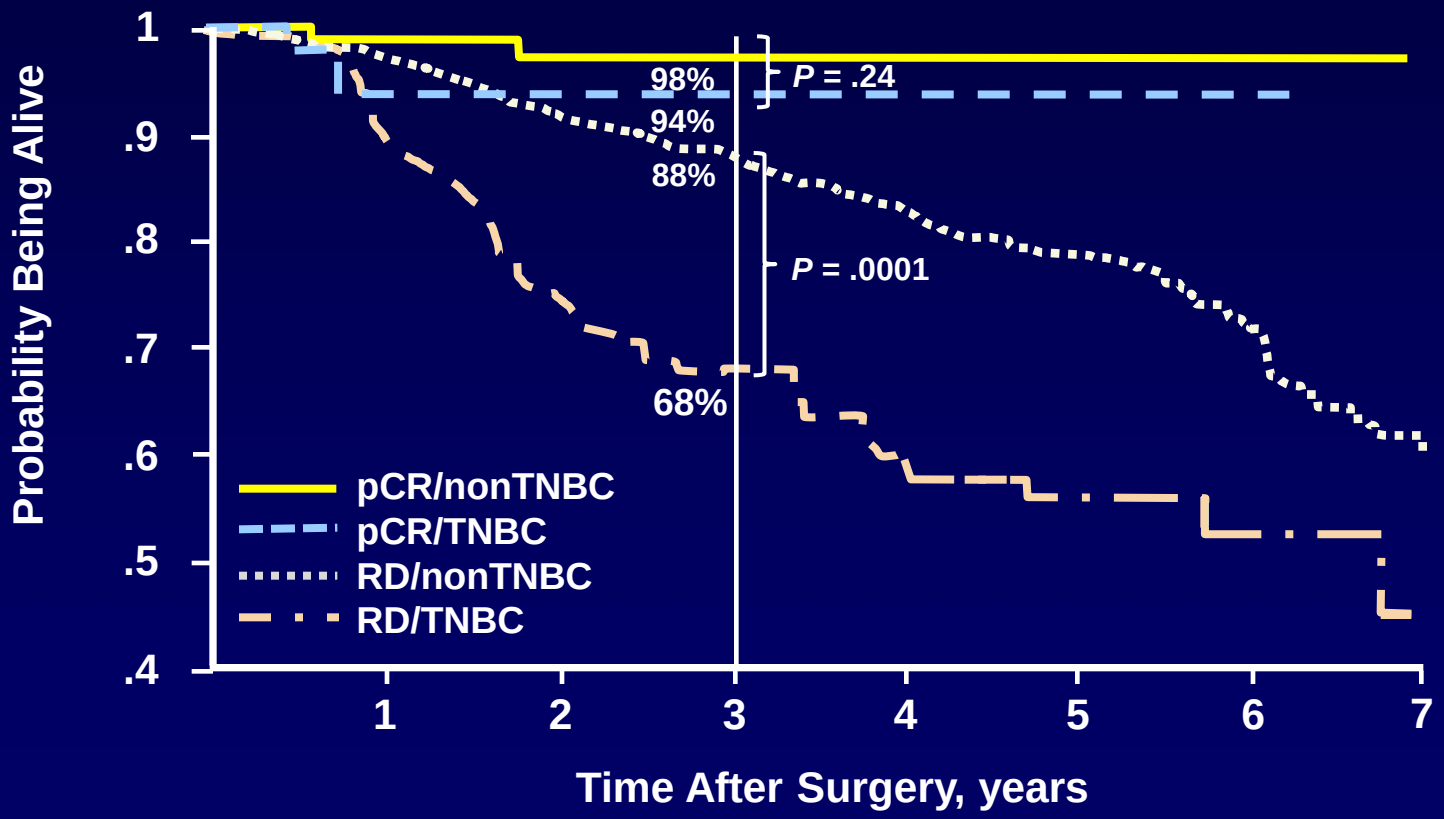
Do you believe that dual HER2 blockade combined with chemotherapy is the best strategy for neoadjuvant therapy in a patient with operable HER2-positive breast cancer?



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

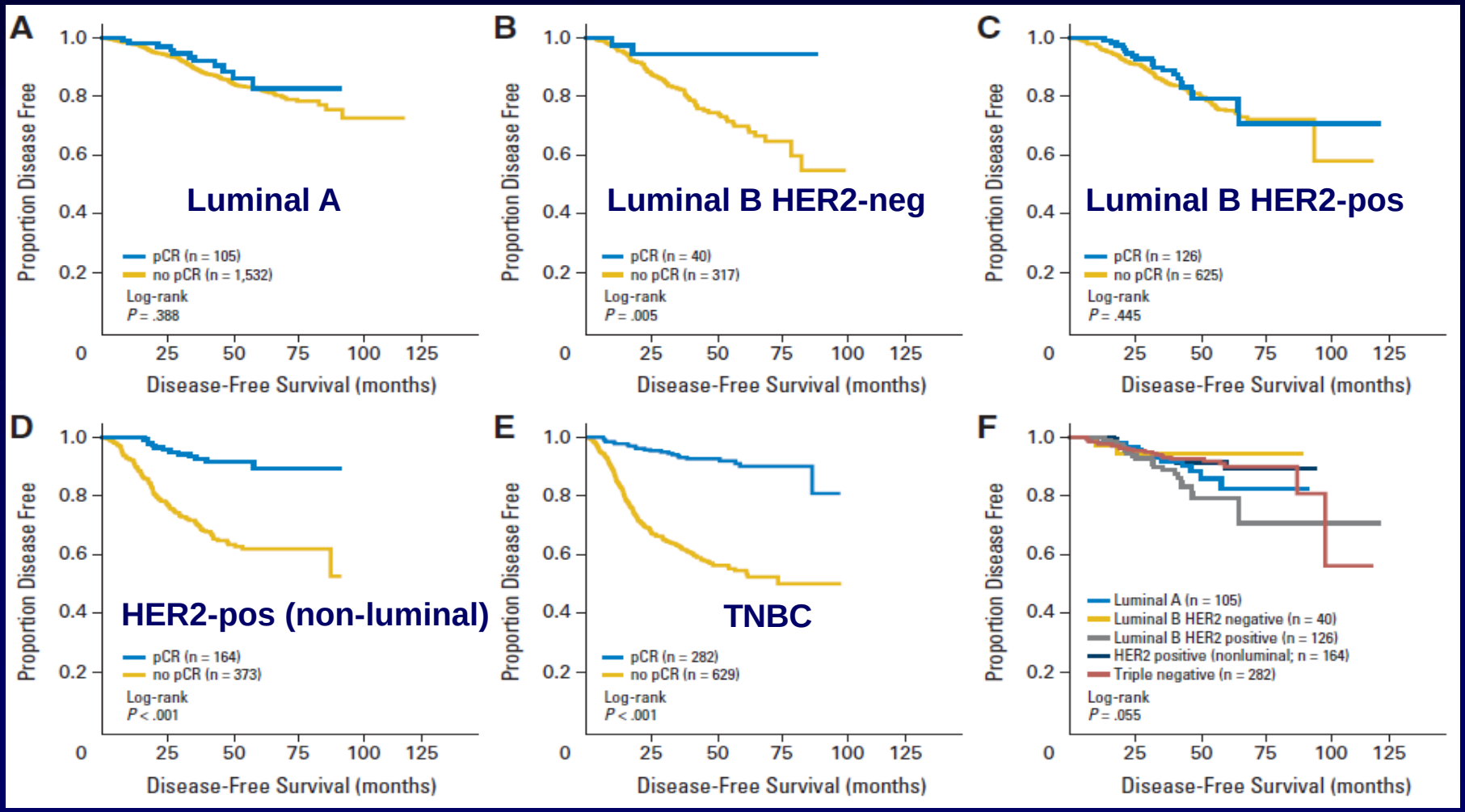
Javier Cortés, MD, PhD
Vall d'Hebron University Hospital
Barcelona, Spain

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



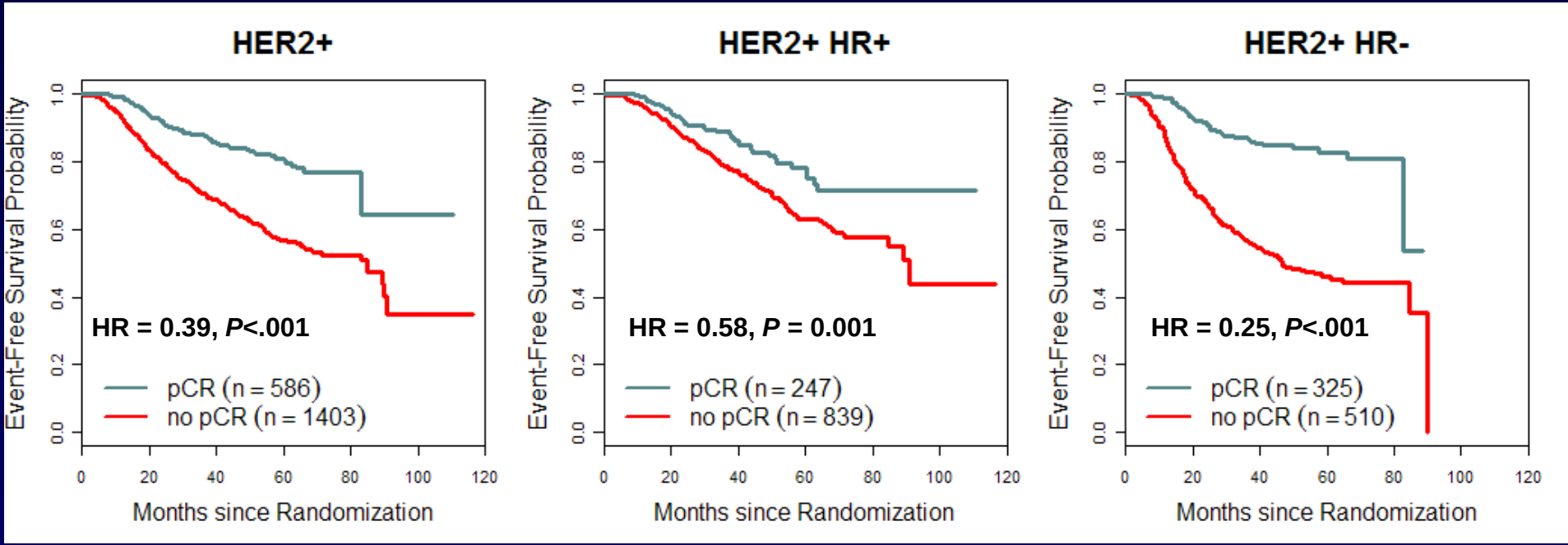
Liedtke C, et al. *J Clin Oncol*. 2008;26(8):1275-1281.

pCR and Prognosis by Subtype (N = 4193)



von Minckwitz G, et al. *J Clin Oncol*. 2012;30(15):1796-1804.

Association of pCR With EFS in HER2+ Subtype



pCR = ypT0/is ypN0

Cortazar P, et al. *Lancet*. 2014;384(9938):164-172.

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:

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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

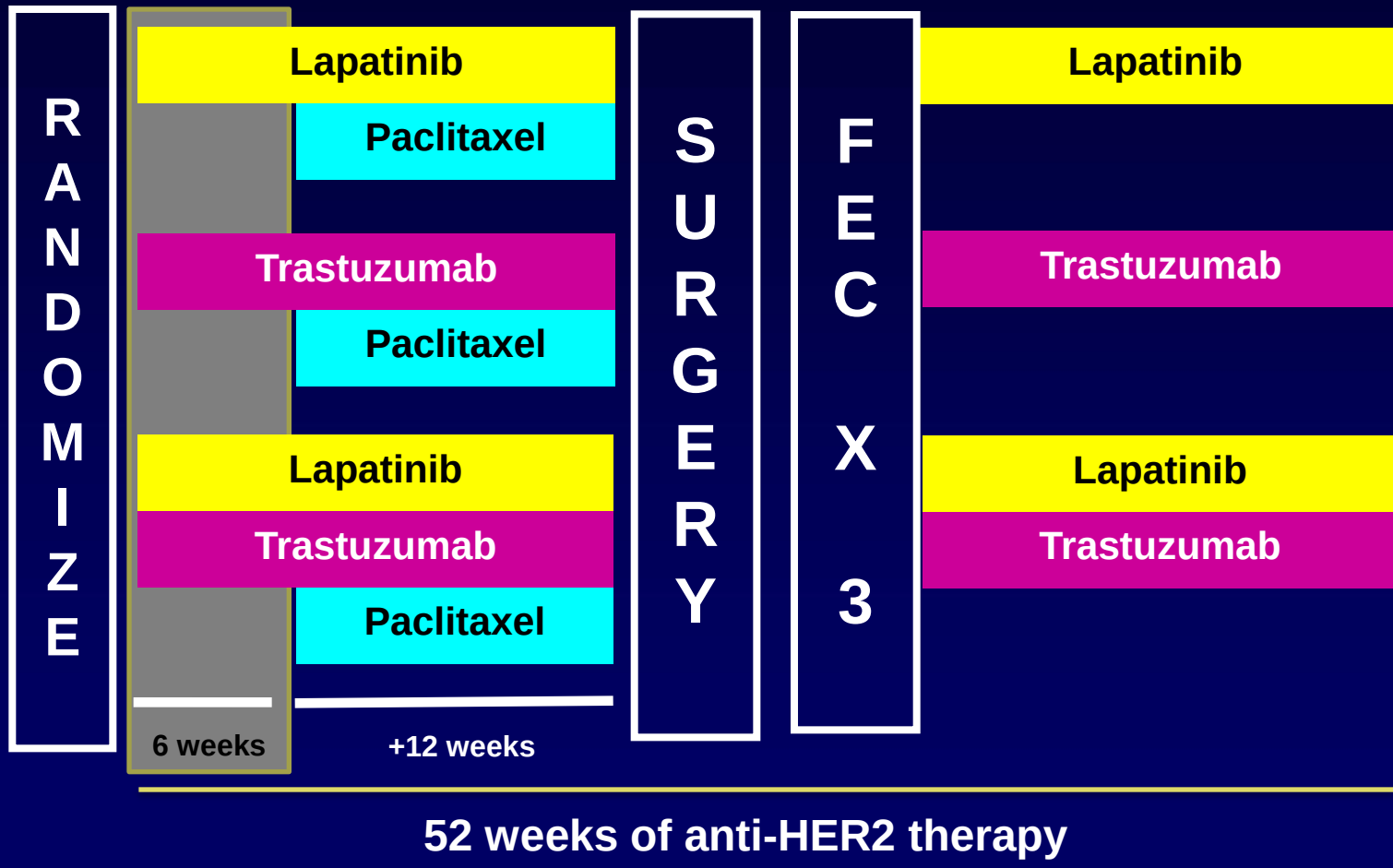
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2012
Clinical/Medical

NeoALTTO Study Design

Eligibility
- Invasive operable HER2+ breast cancer
- Tumor >2 cm (inflammatory breast cancer excluded)
- LVEF ≥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



LVEF, left ventricular ejection fraction

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

Study Objectives

Primary endpoint

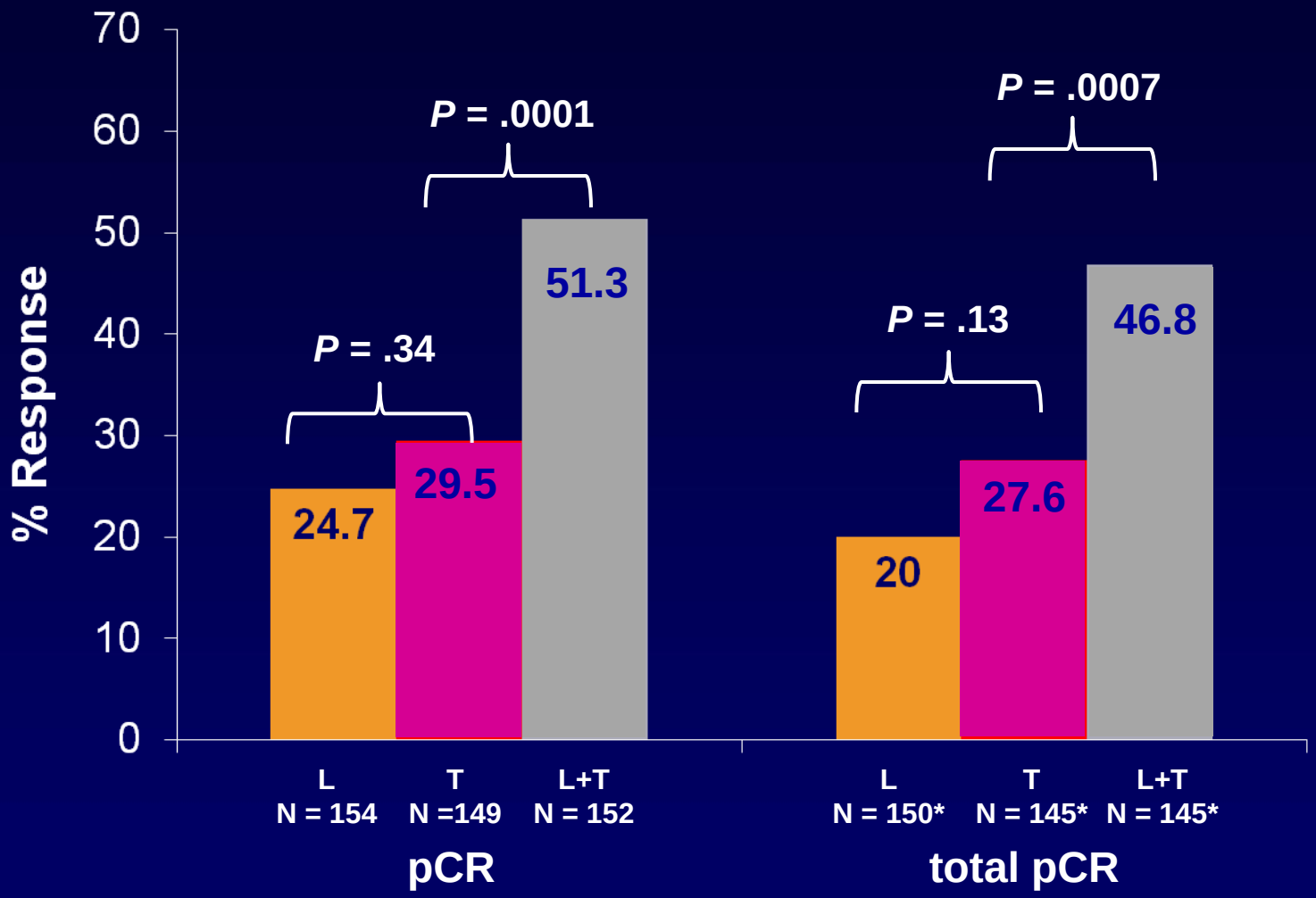
- **pCR: Defined according to the National Surgical Adjuvant Breast Project guidelines as no invasive cancer in the breast or only noninvasive *in situ* cancer in the breast specimen[1,2]**

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**

1. Fisher B, et al. *J Clin Oncol.* 1997;15(7):2483-2493. 2. Fisher ER, et al. *Cancer.* 2002;95(4):681-695.
3. Baselga J, et al. *Lancet.* 2012;379(9816):633-640.

NeoALTTO: pCR and Total pCR

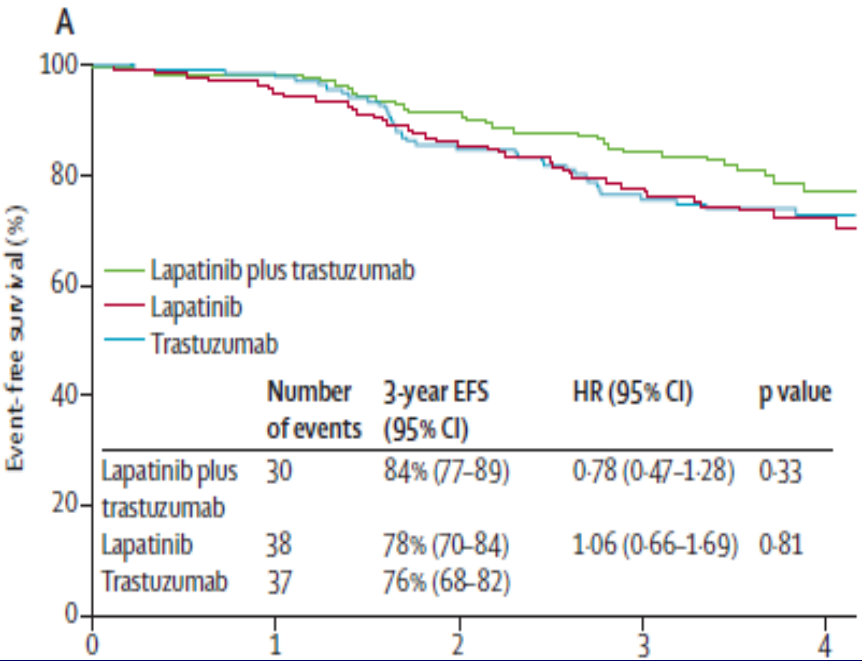


*Excludes 15 patients with nonevaluable nodal status
L, lapatinib; T, trastuzumab

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

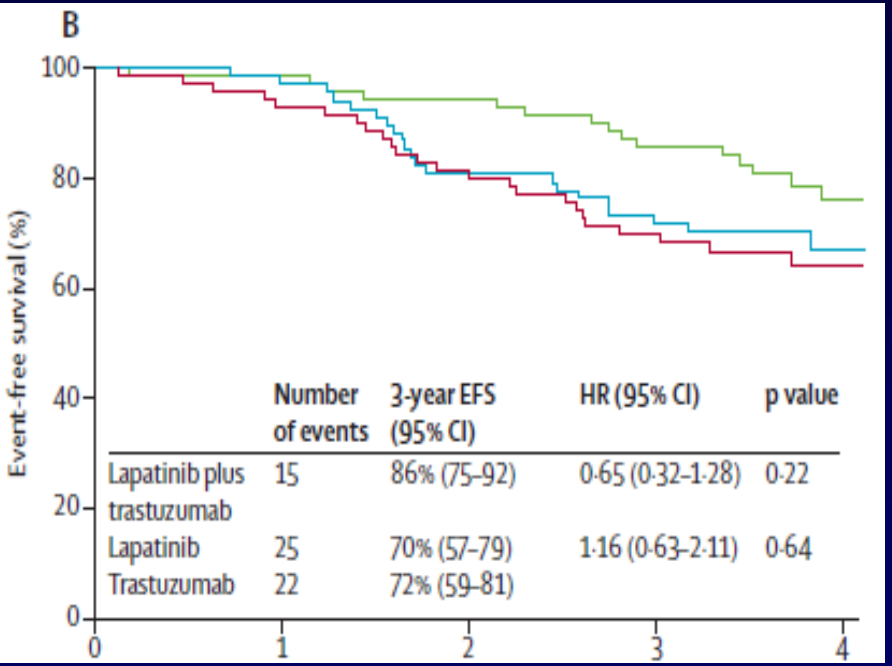
NeoALTTO: DFS

ER+



	Number of events	3-year EFS (95% CI)	HR (95% CI)	p value
Lapatinib plus trastuzumab	30	84% (77–89)	0·78 (0·47–1·28)	0·33
Lapatinib	38	78% (70–84)	1·06 (0·66–1·69)	0·81
Trastuzumab	37	76% (68–82)		

ER-

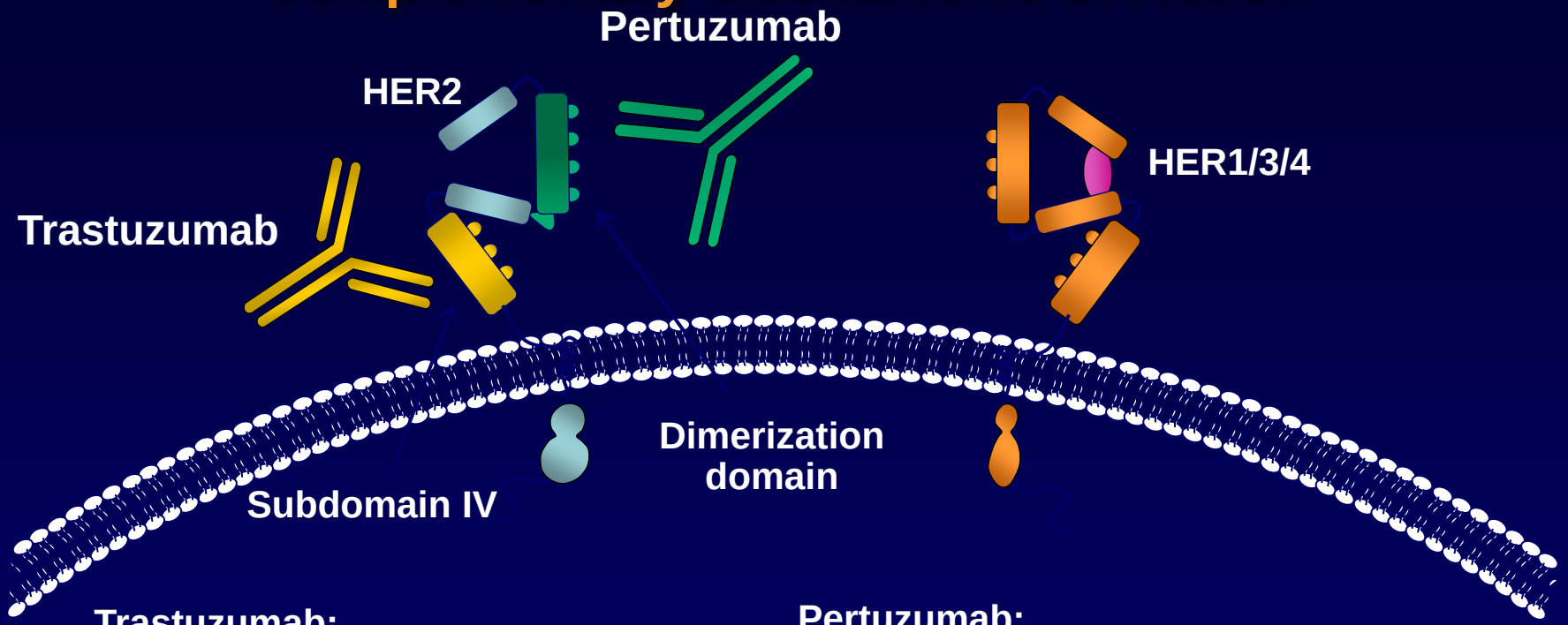


	Number of events	3-year EFS (95% CI)	HR (95% CI)	p value
Lapatinib plus trastuzumab	15	86% (75–92)	0·65 (0·32–1·28)	0·22
Lapatinib	25	70% (57–79)	1·16 (0·63–2·11)	0·64
Trastuzumab	22	72% (59–81)		

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

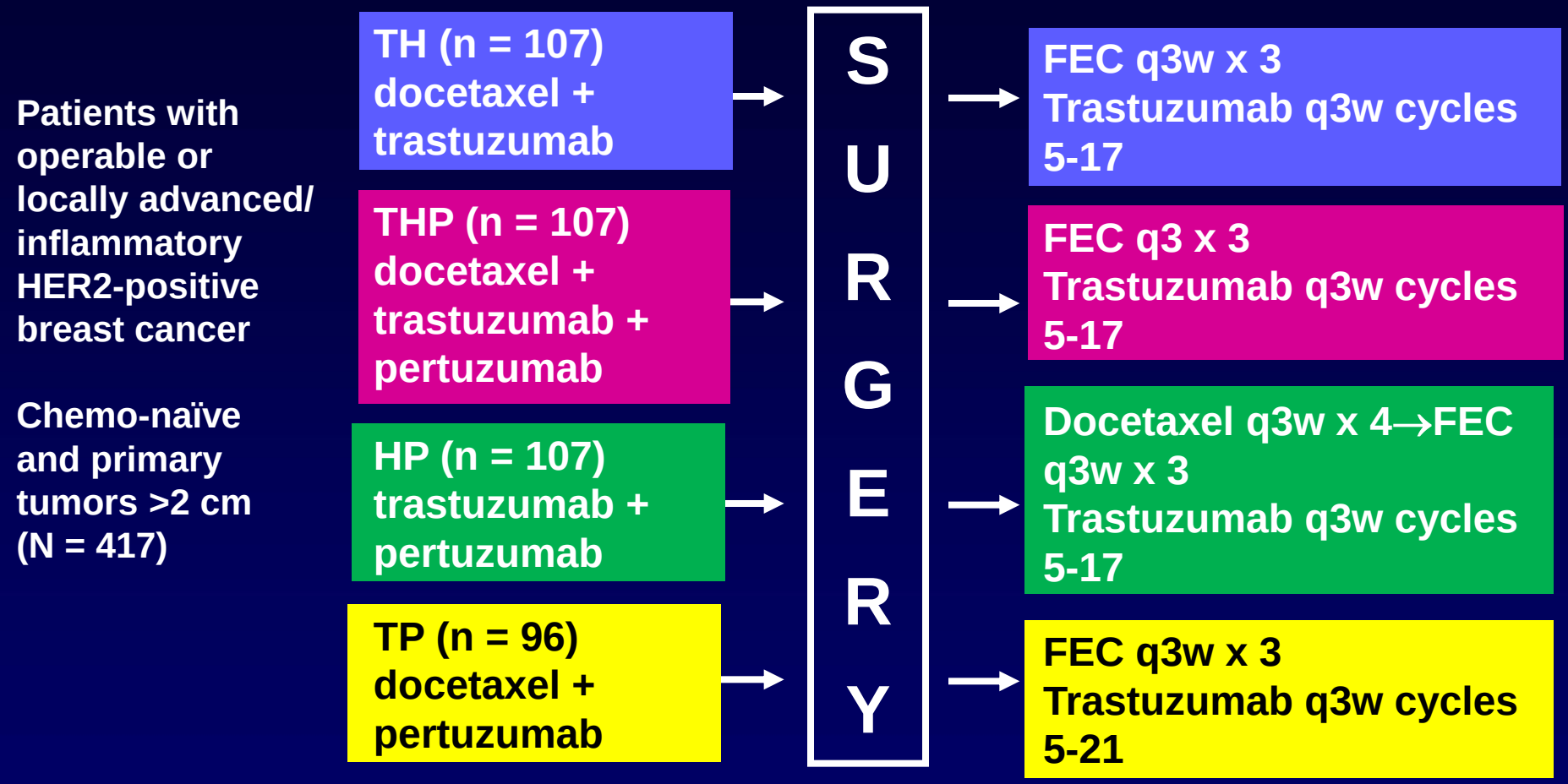
Pertuzumab:

- 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. 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.

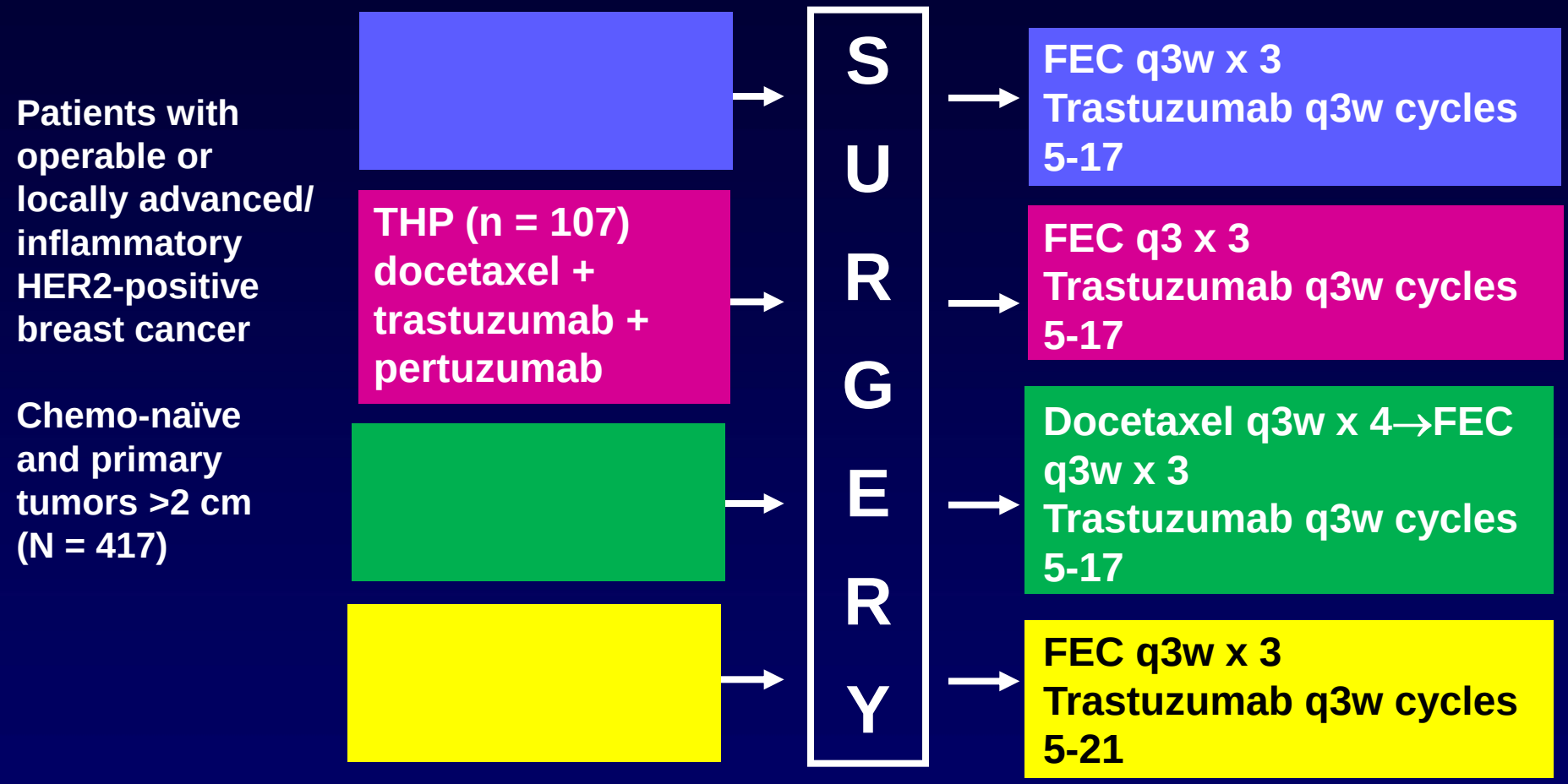
NeoSphere Study Design



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

Gianni L, et al. *Lancet Oncol.* 2012;13(1):25-32.

NeoSphere Study Design



Gianni L, et al. *Lancet Oncol.* 2012;13(1):25-32.

Study Objectives

Primary endpoint: Comparison of pCR rates

- TH vs THP

Exploratory analyses

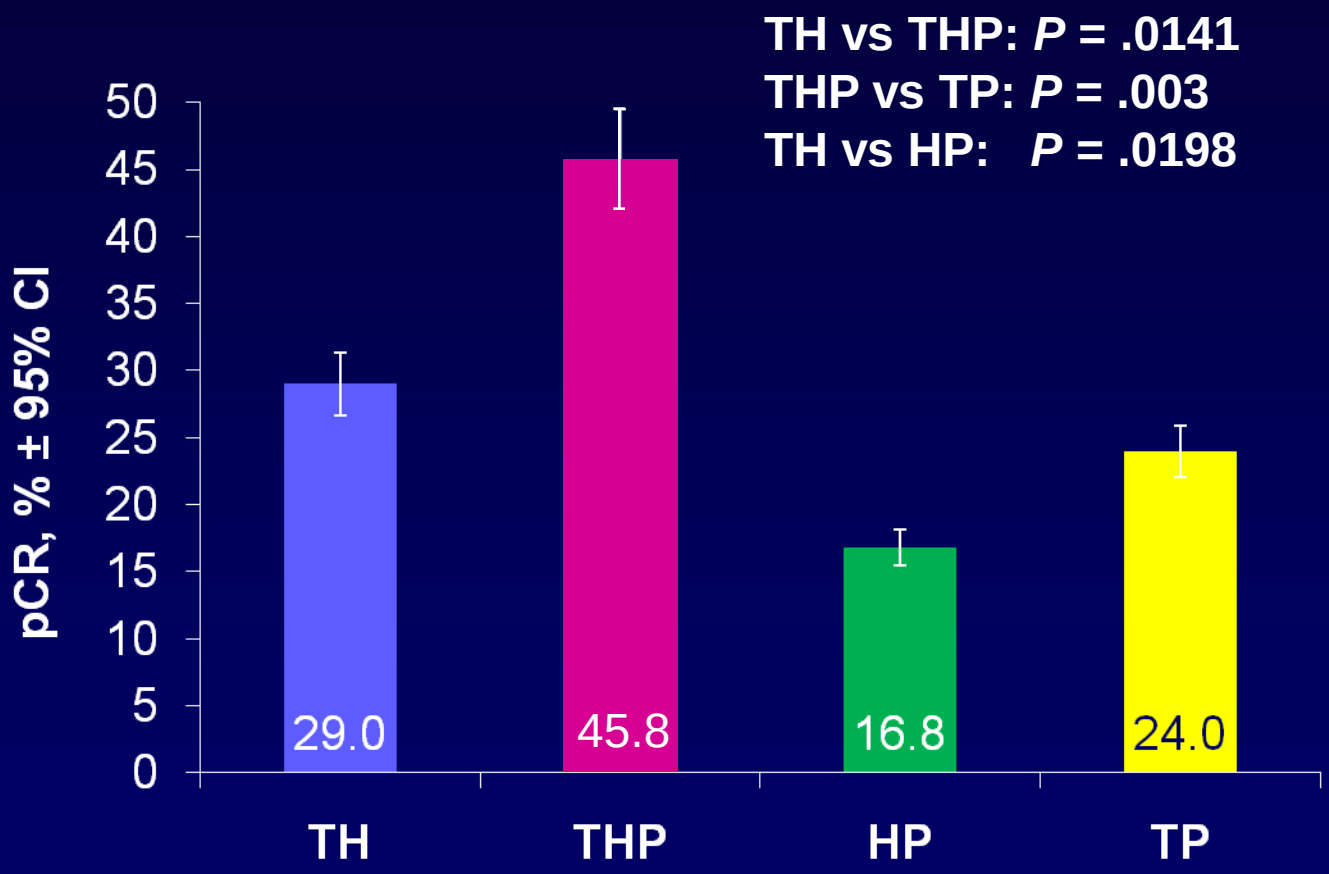
- TH vs HP
- THP vs TP

Secondary endpoints

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

Gianni L, et al. *Lancet Oncol.* 2012;13(1):25-32.

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



Gianni L, et al. *Lancet Oncol.* 2012;13(1):25-32.

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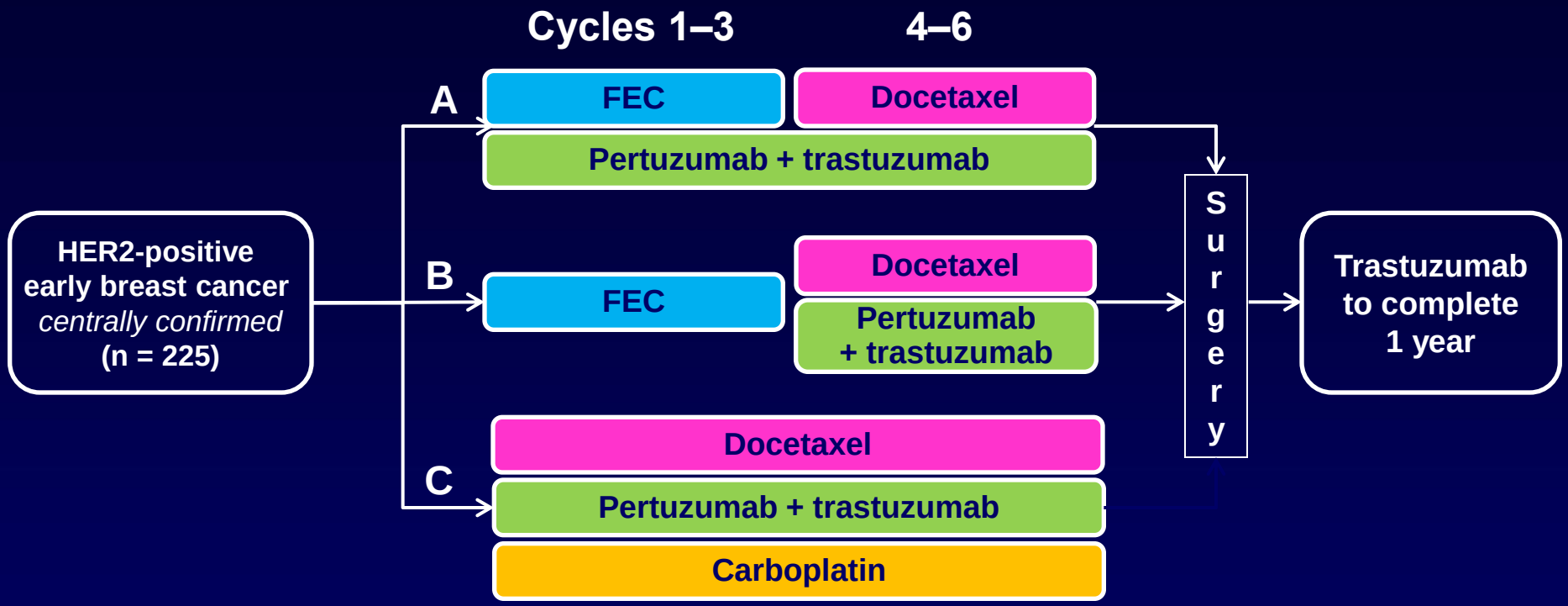
TRYPHAENA: Study Design



Study dosing q3w

- **FEC** 500 mg/m^2, 100 mg/m^2, 600 mg/m^2
- **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^2 (escalating to 100 mg/m^2 if tolerated, in arms A and B only)

AUC, area under the concentration-time curve

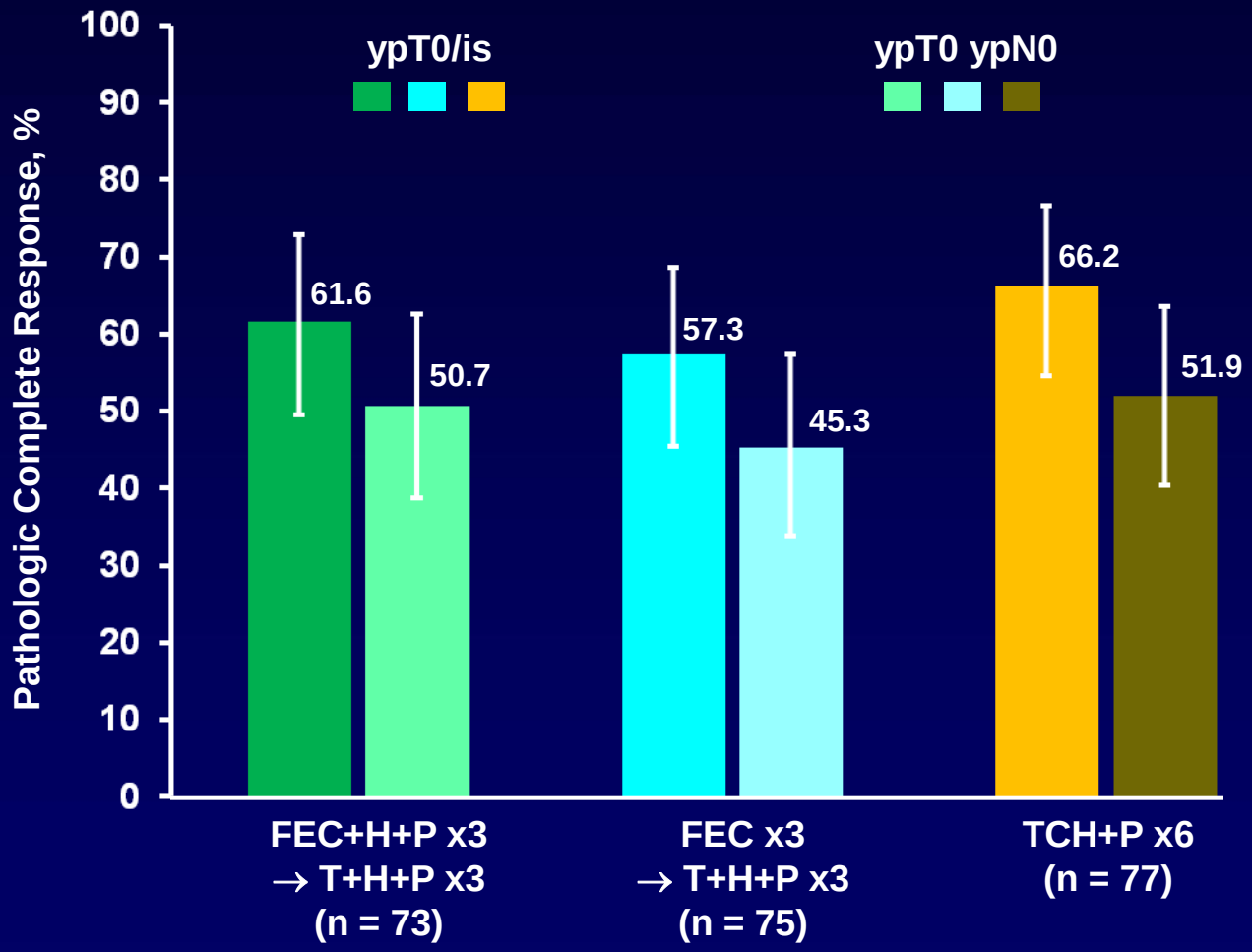
Schneeweiss A, et al. *Ann Oncol*. 2013;24(9):2278-2284.

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)

Schneeweiss A, et al. *Ann Oncol*. 2013;24(9):2278-2284.

TRYPHAENA: pCR



Schneeweiss A, et al. *Ann Oncol*. 2013;24(9):2278-2284.

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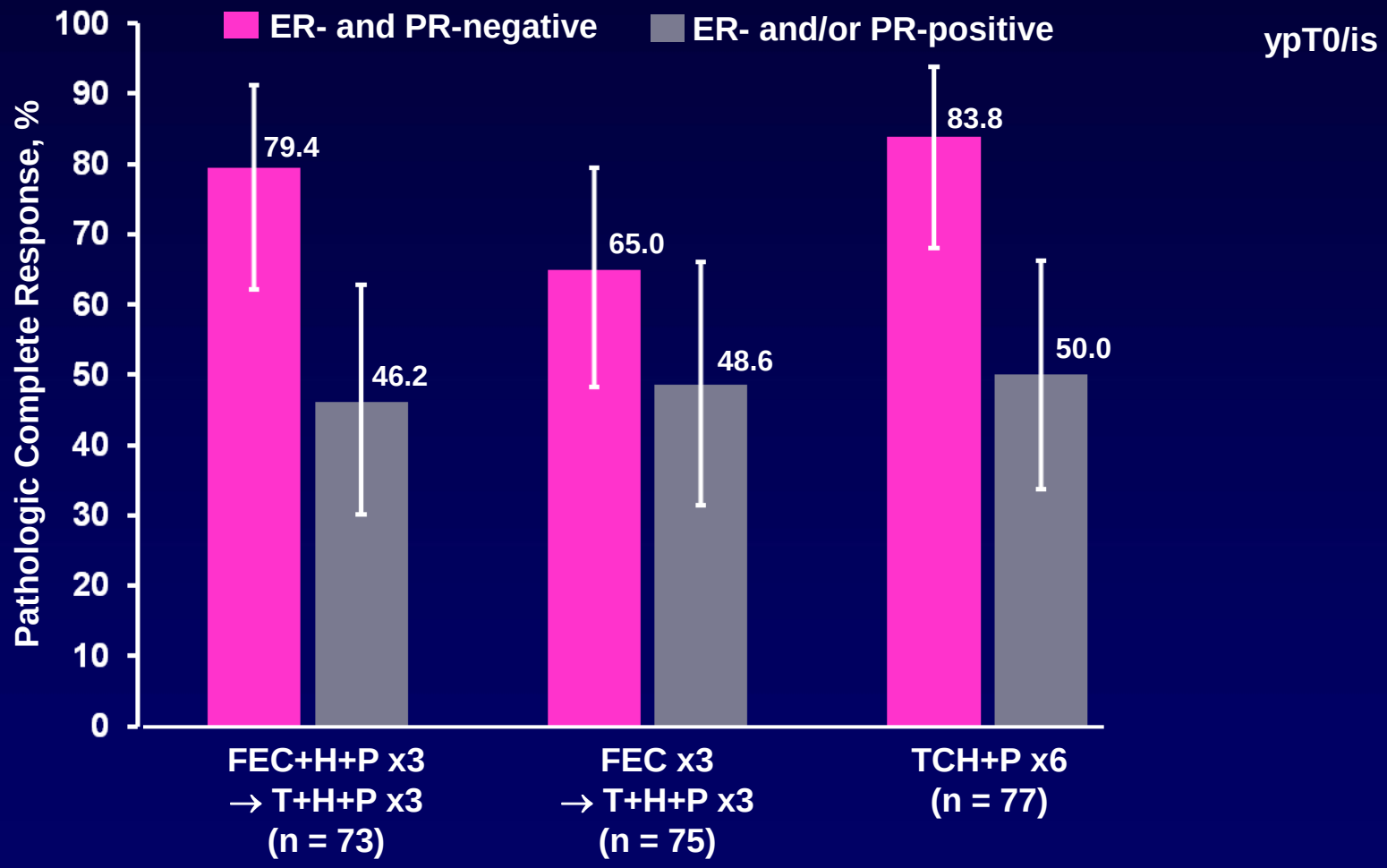
TRYPHAENA: pCR by Estrogen / Progesterone Receptor Status



Schneeweiss A, et al. *Ann Oncol*. 2013;24(9):2278-2284.

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

My Opinion

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**

RAISING THE BAR

IN BREAST CANCER CARE:

Answering Clinically Relevant Questions