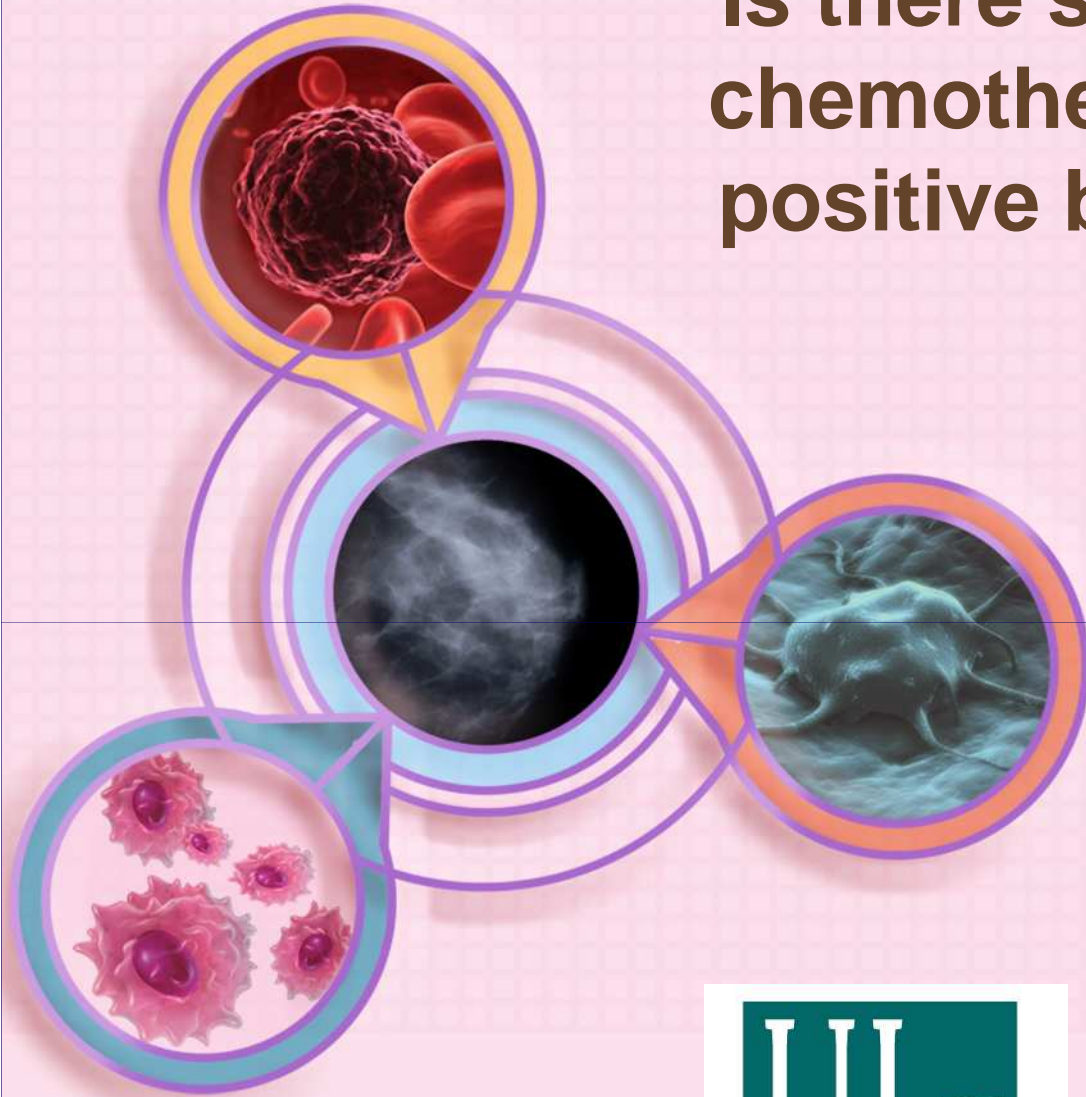
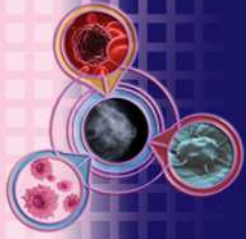


# Is there still a place for chemotherapy in the HER-2 positive breast cancer?

Joelle COLLIGNON

Guy JERUSALEM





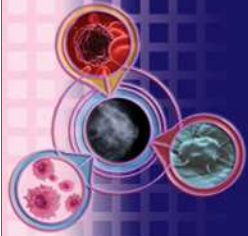
## **HER2: role in breast cancer**

**Human epidermal growth factor receptor 2 (HER2)  
is a transmembrane protein**

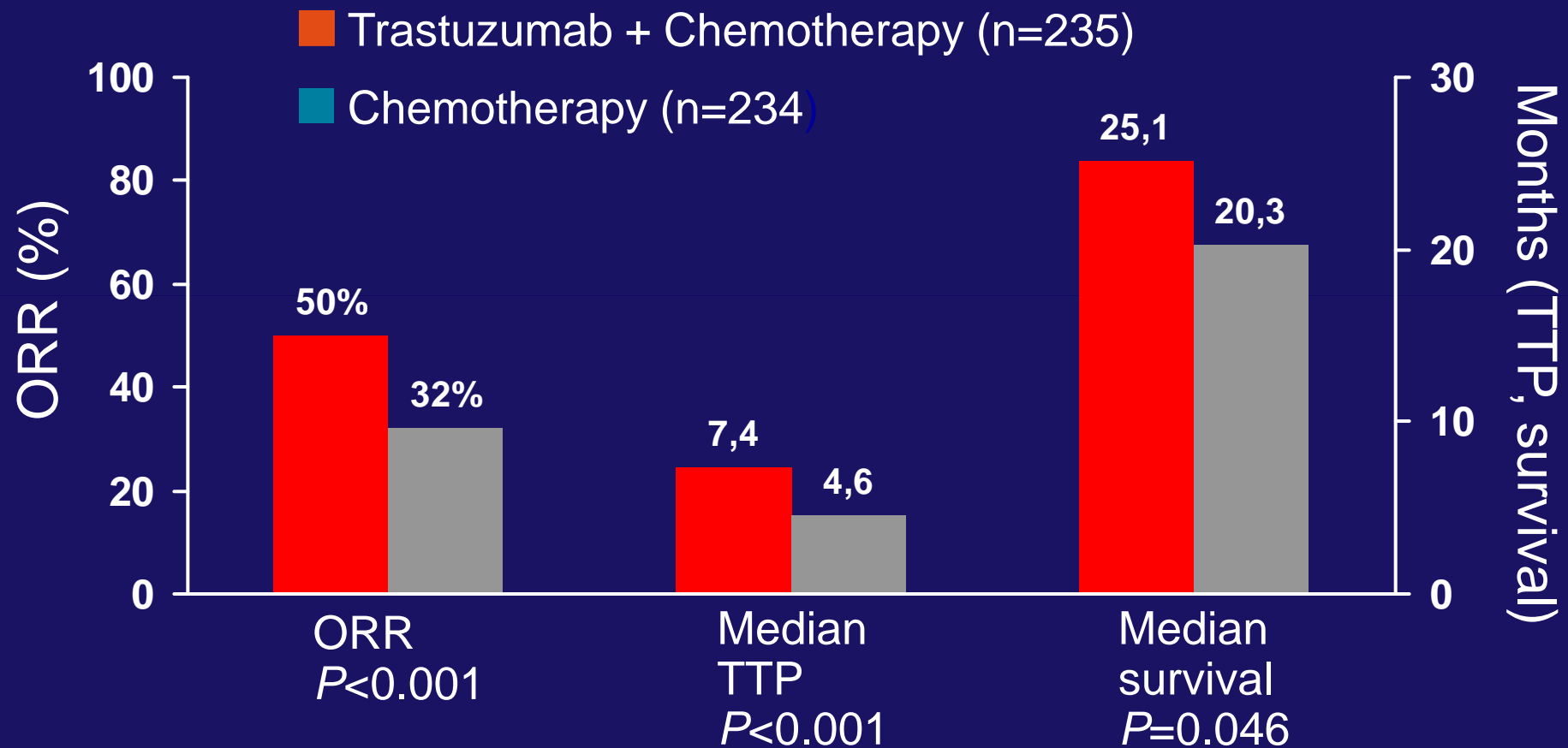
**Overexpression of HER2 occurs in 15% of breast cancers**

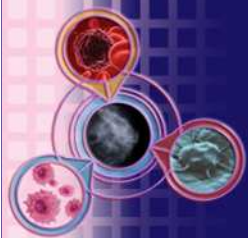
**HER2 positivity is associated with**

- aggressive disease**
- a high risk of relapse**
- poor survival**

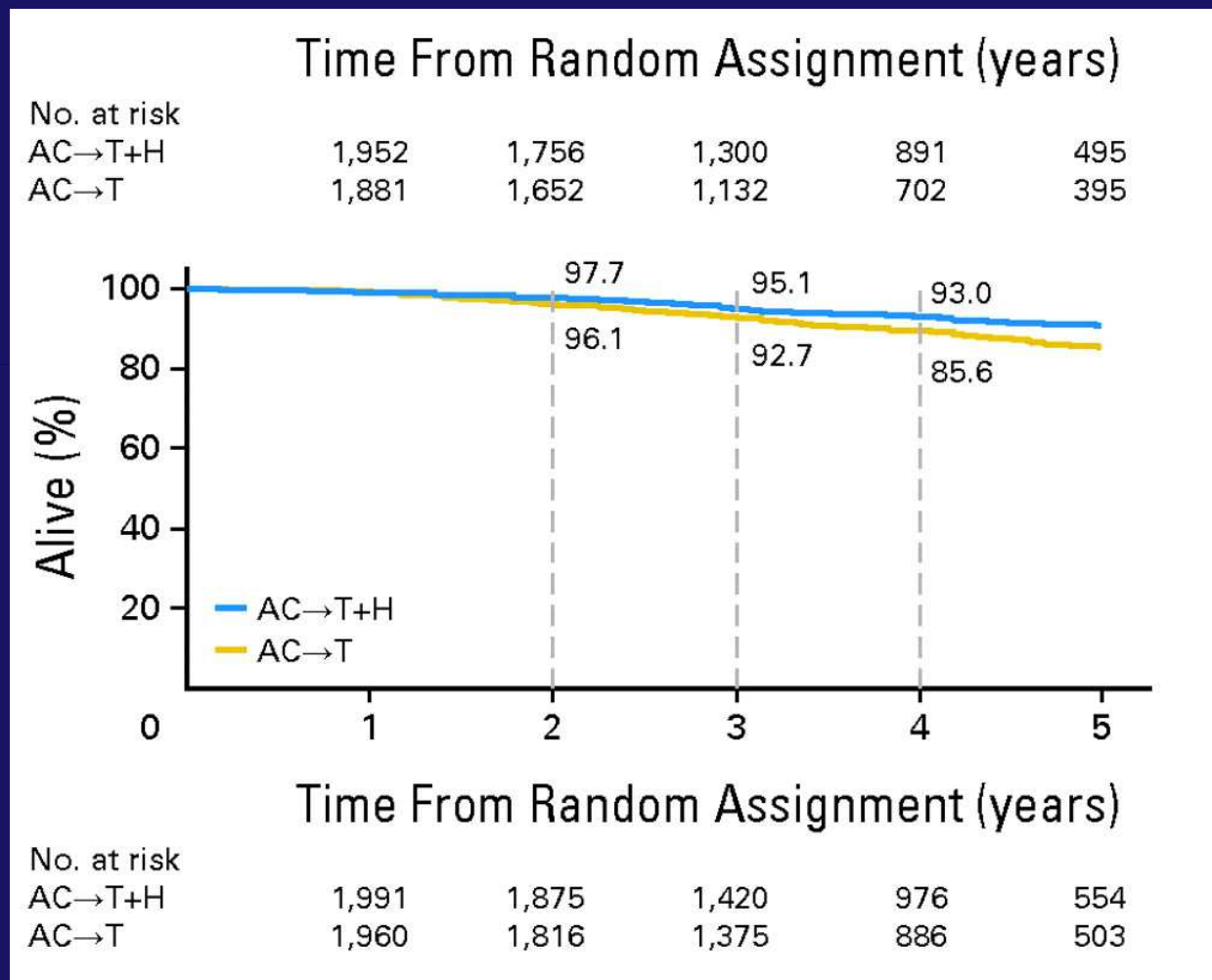


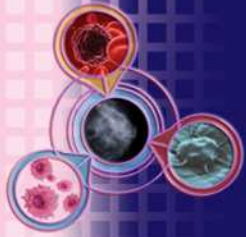
# Chemotherapy +/- Trastuzumab in Metastatic Breast Cancer



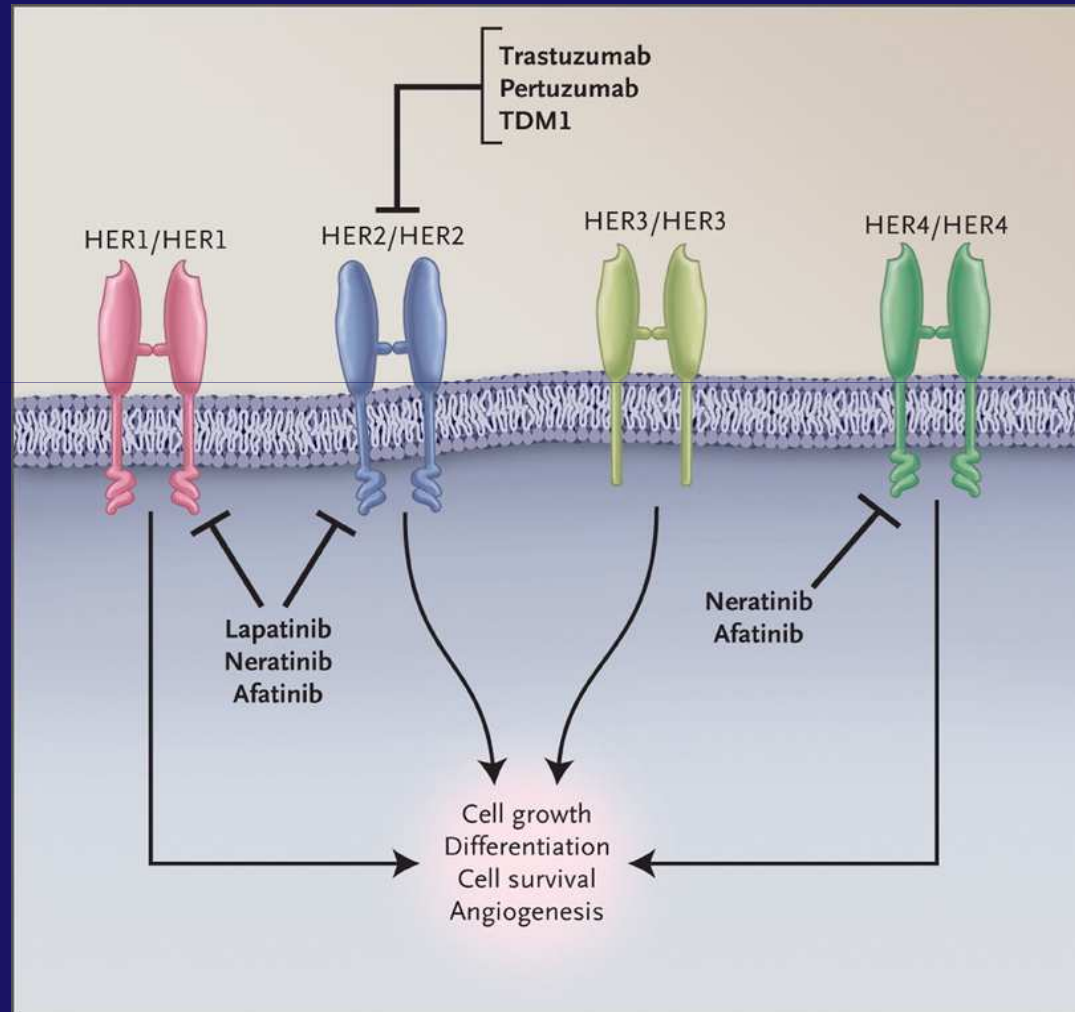


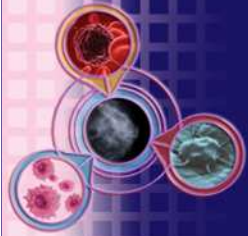
# 4 years follow-up joint analysis NCCTG N9831 and NSABP B-31 Kaplan-Meier estimates of overall survival





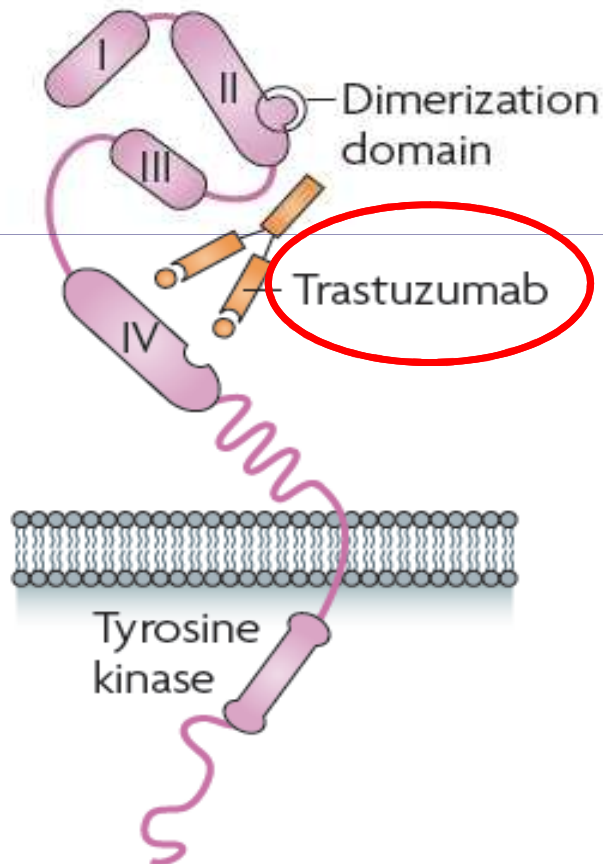
# Human Epidermal Growth Factor Receptor (HER) Family of Receptors and Therapeutic Agents Currently Available or in Development.



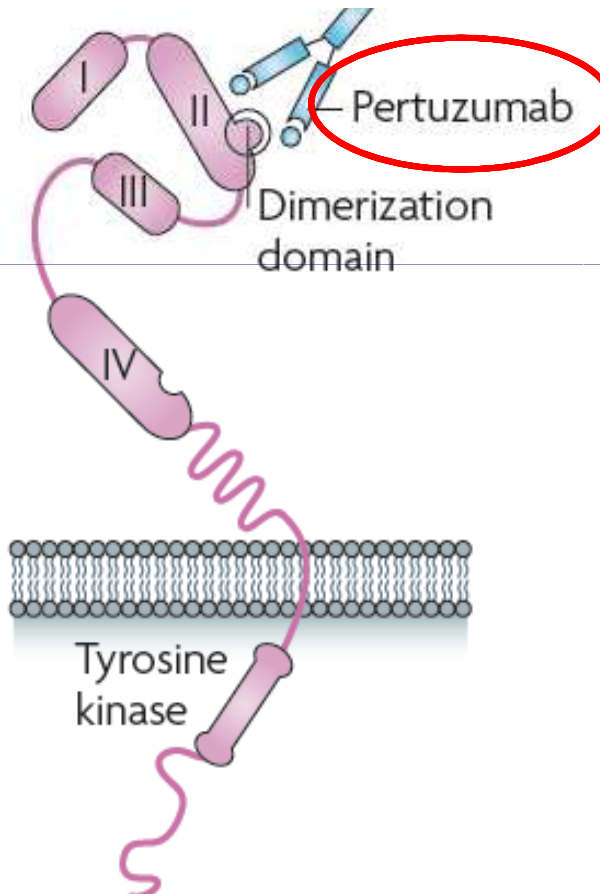


# ANTI-HER2 THERAPIES

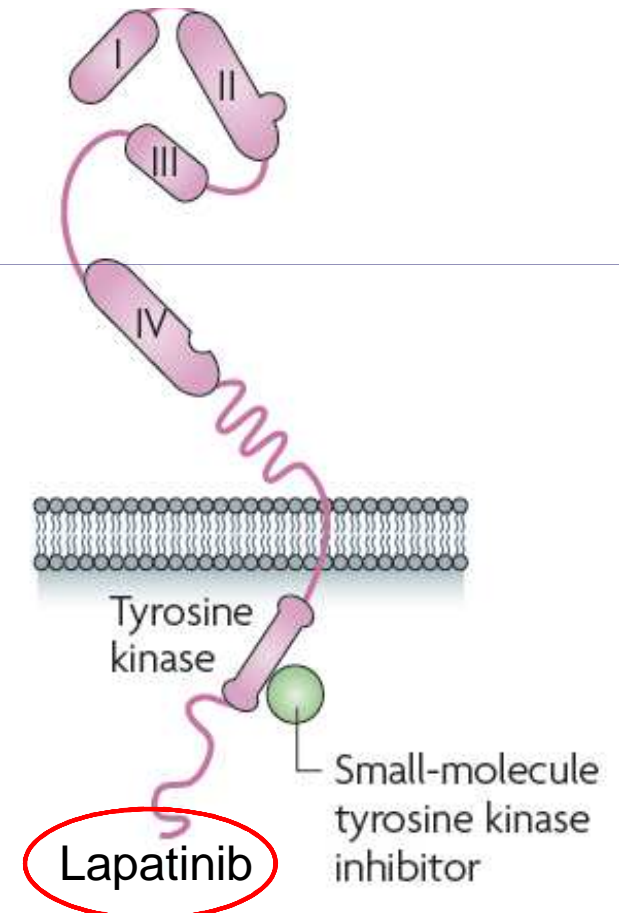
A Inhibition through direct antibody binding

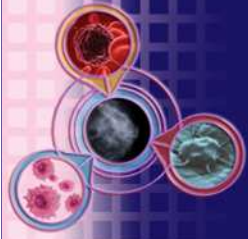


B Inhibition through dimerisation inhibition



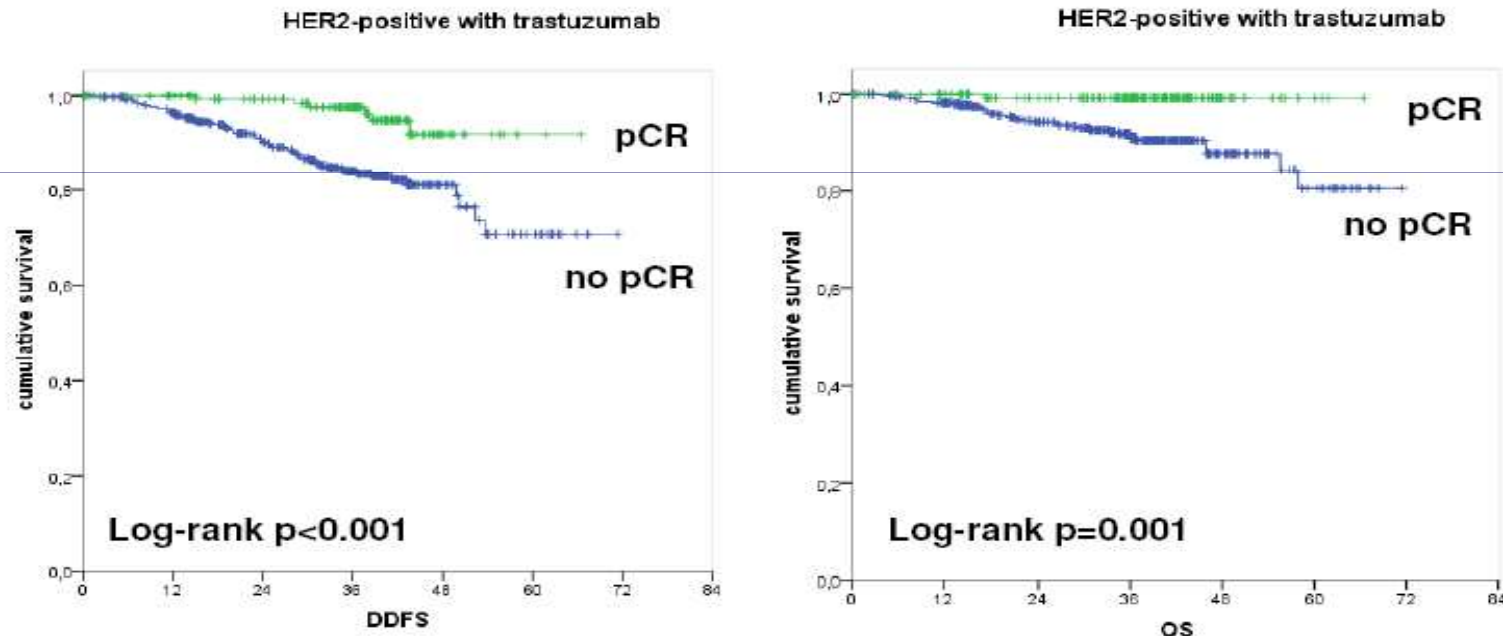
C Inhibition of tyrosine kinase activity

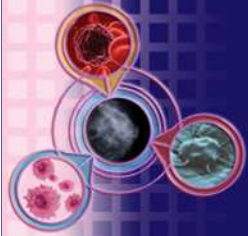




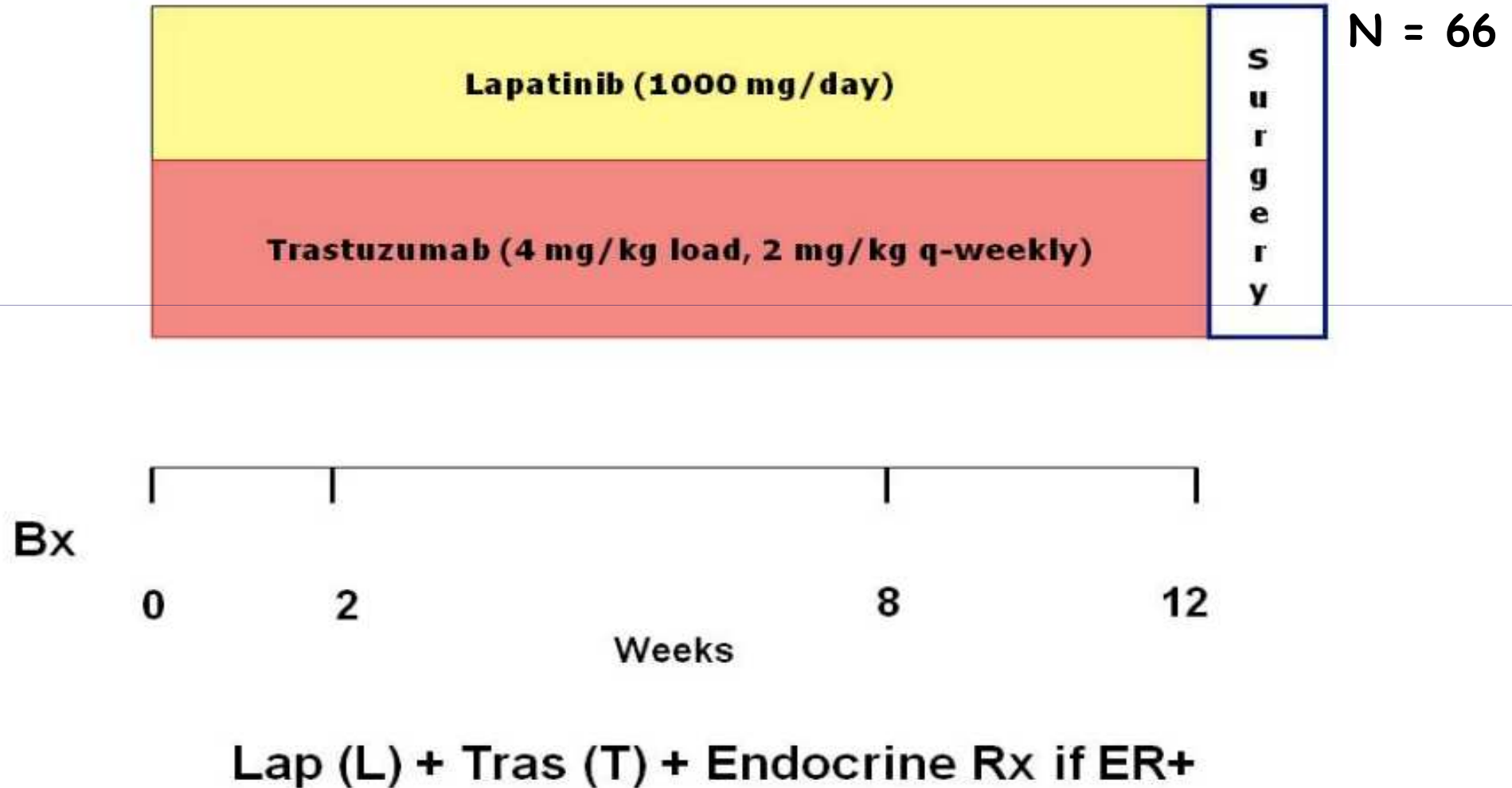
# NEOADJUVANT TREATMENT: pCR is predictive of outcome in HER positive disease

## DDFS and OS by pCR – HER2-positive with Trastuzumab

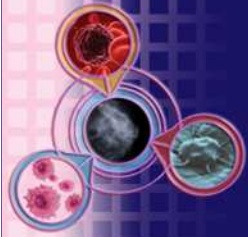




# NEOADJUVANT TREATMENT WITHOUT CHEMOTHERAPY

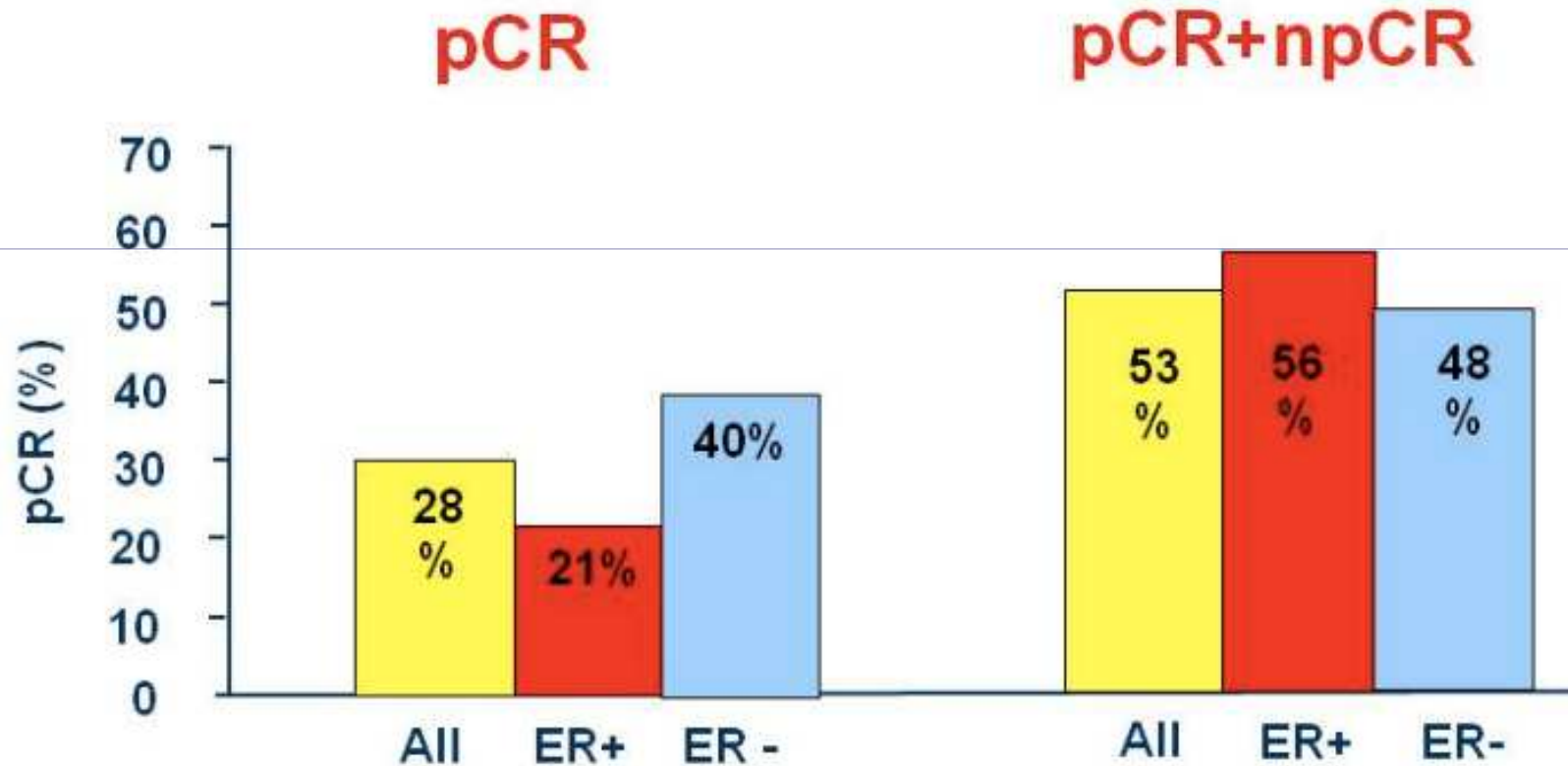


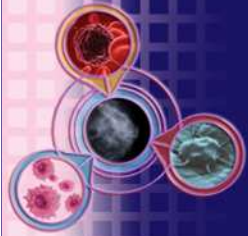




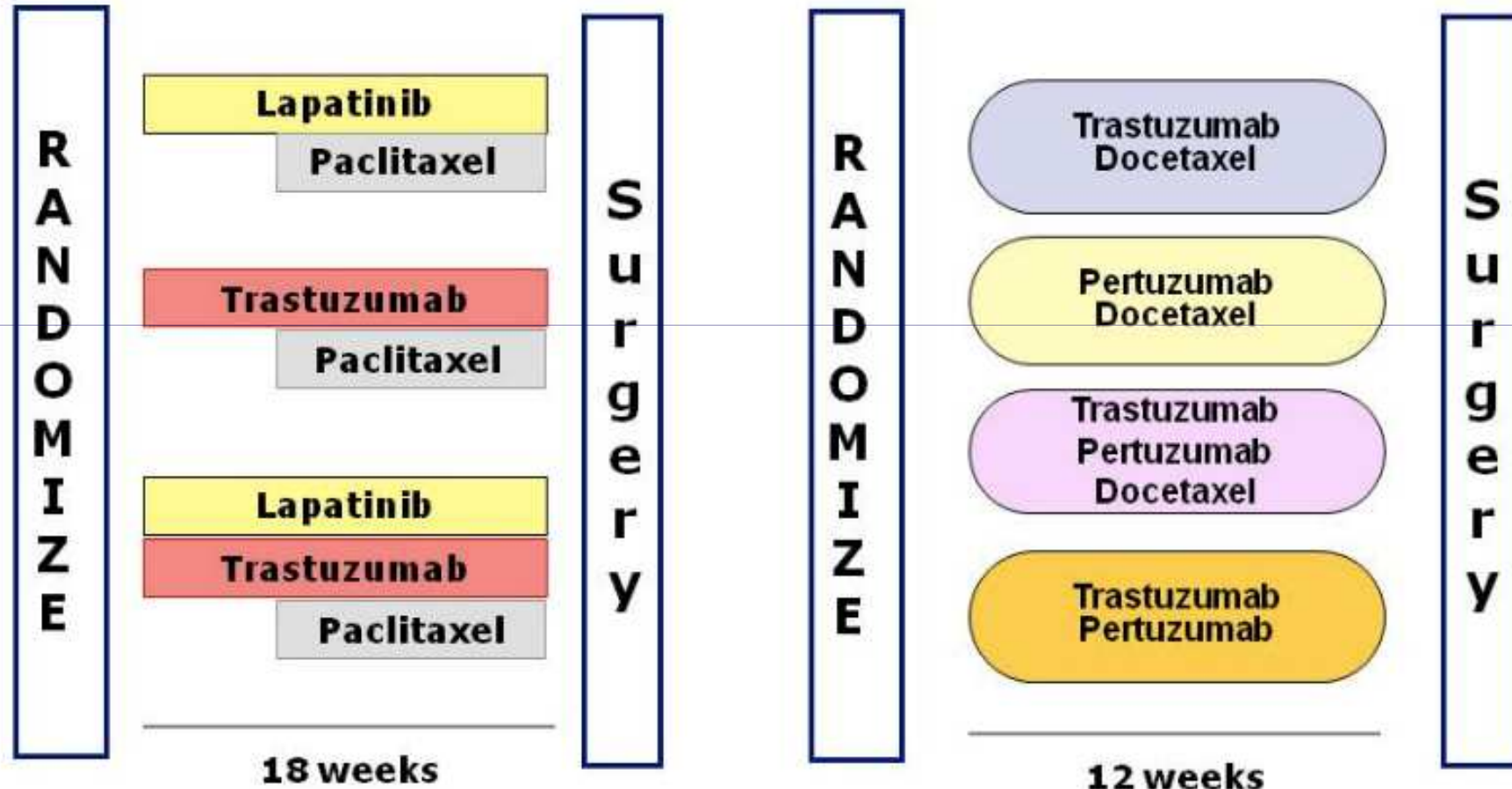
# NEOADJUVANT TREATMENT

## Pathologic response



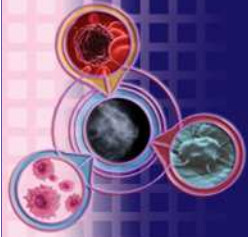


# DUAL Blockade with Taxanes: NeoALLTO and NeoSphere: Study Design

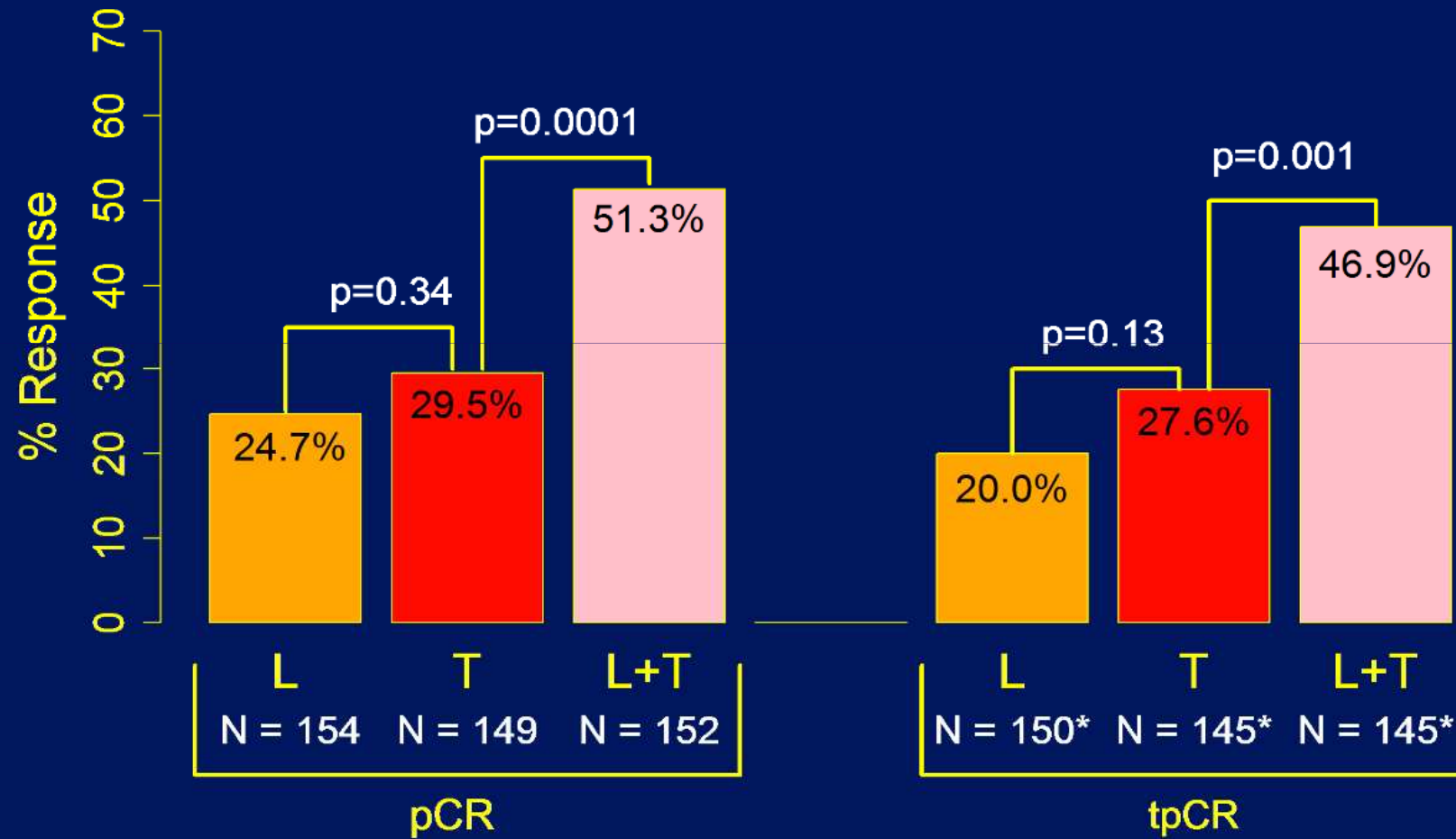


**Neo-Altto**

**Neo-Sphere**



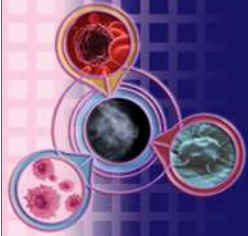
## EFFICACY – pCR and tpCR



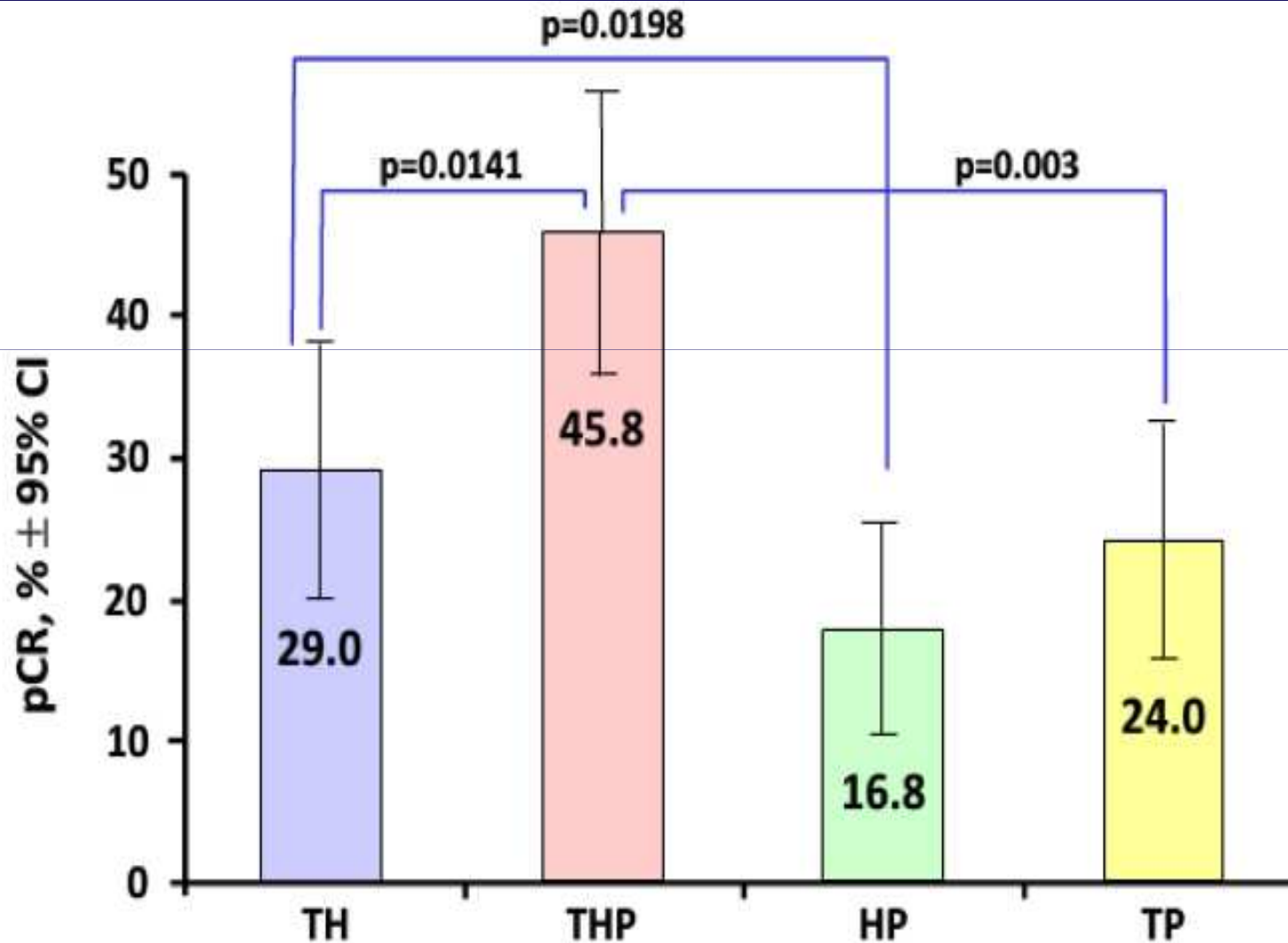
Pathological Complete Response

Locoregional (total) pCR

*Baselga J et al, SABCS, 2010*

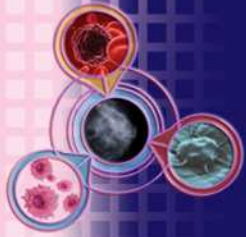


# NeoSphere: Primary endpoint Pathologic complete response

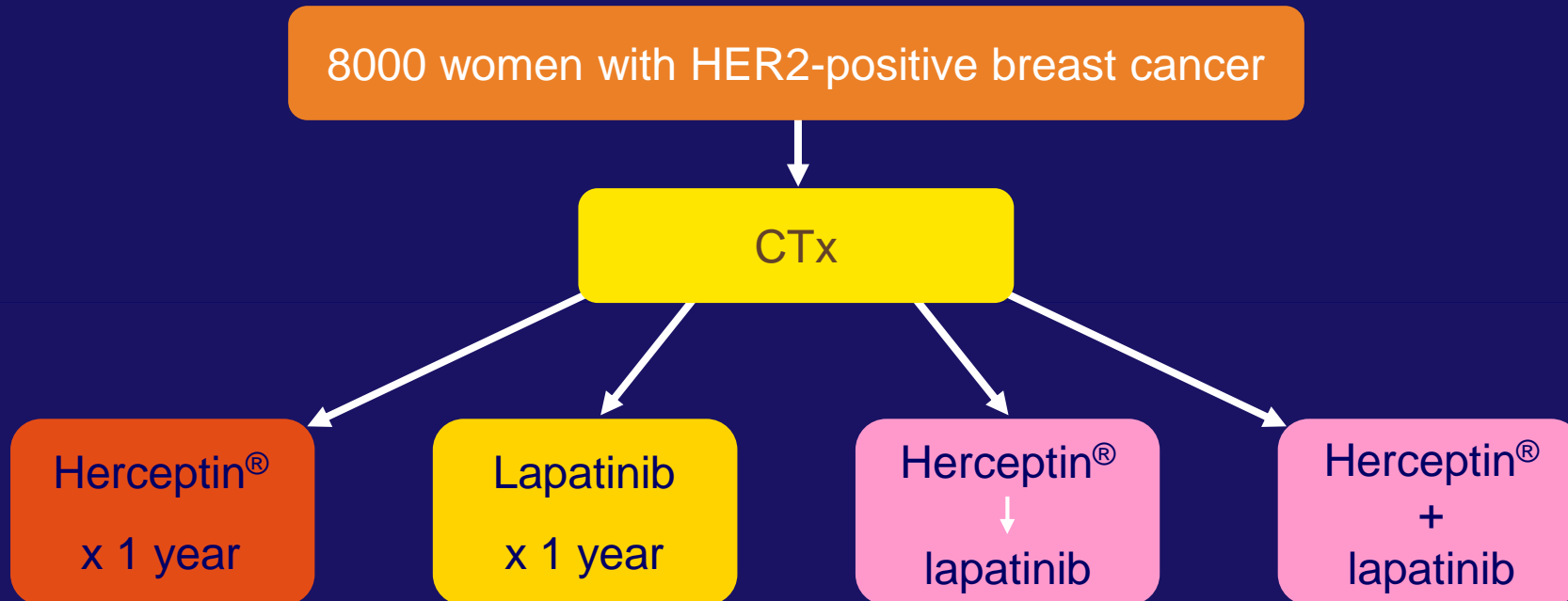


H, trastuzumab; P, pertuzumab; T, docetaxel

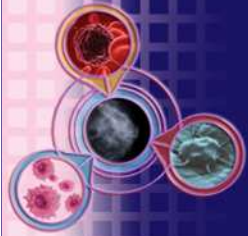
Gianni L, et al. *Lancet Oncol* 2011 DOI:10.1016/S1470-2045(11)70336-9



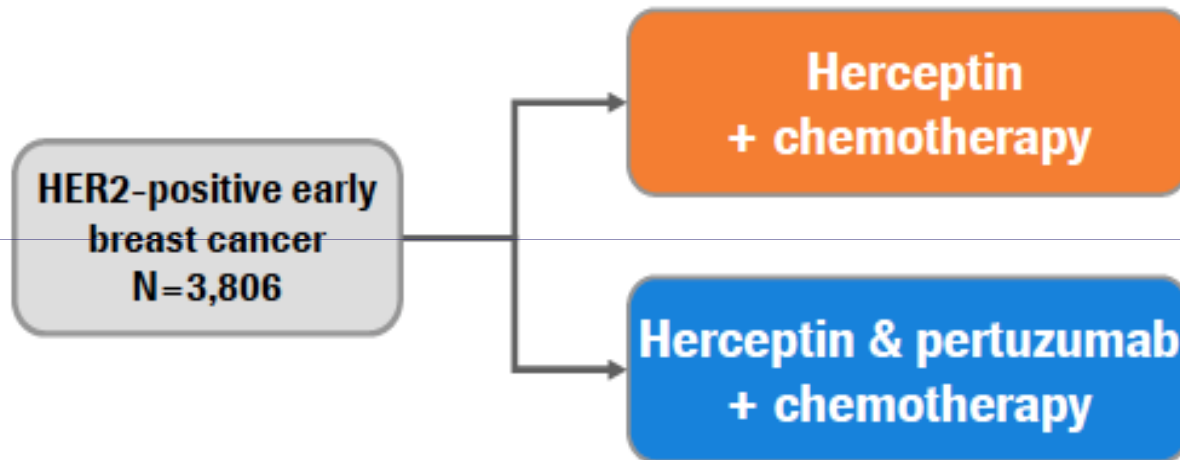
## Adjuvant anti-HER2 therapies will be compared in the ALTTO trial



- Includes translational research, eg tumour and blood collection

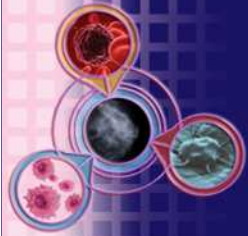


# Trastuzumab and pertuzumab in the adjuvant setting: the APHINITY trial



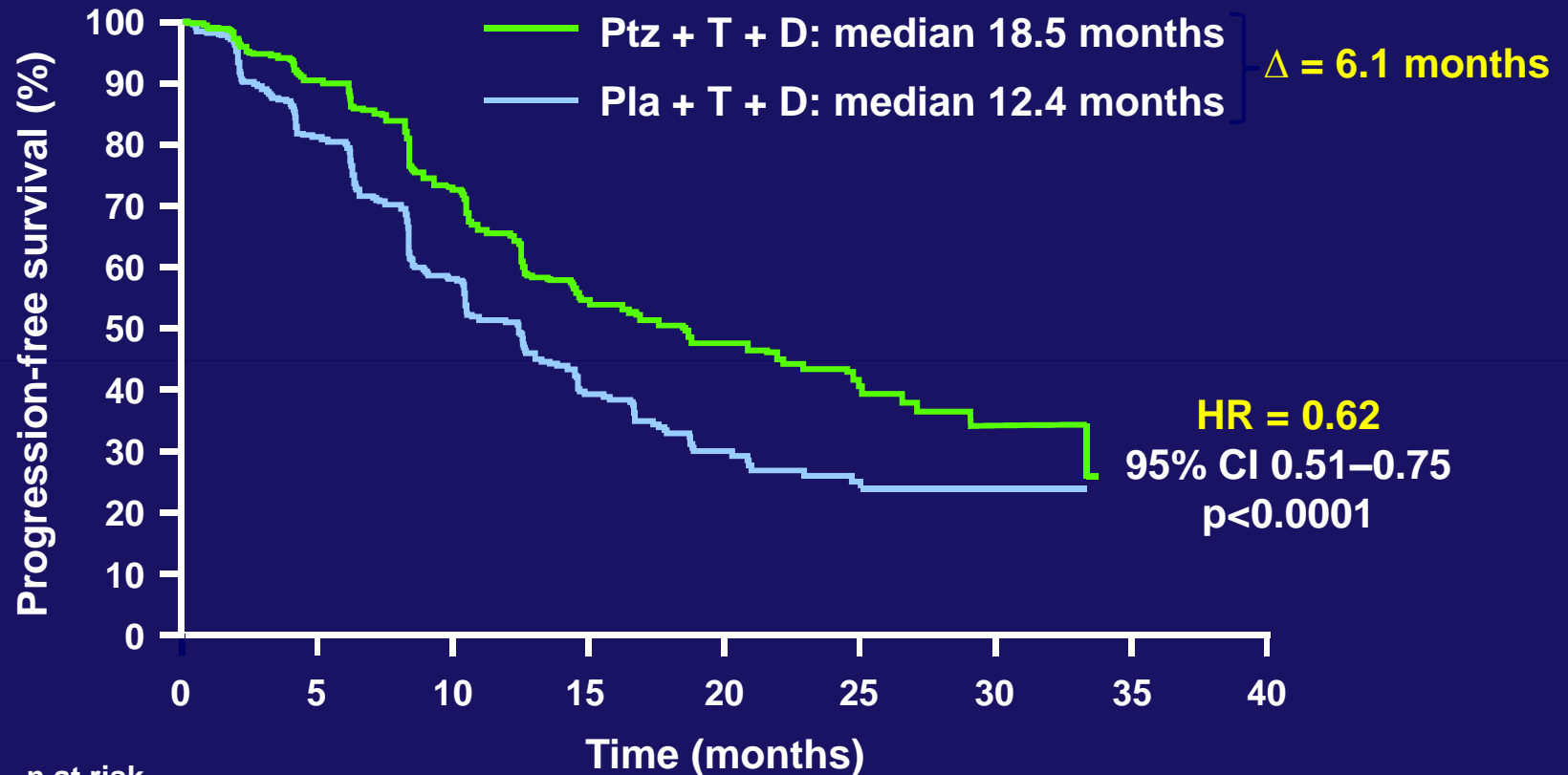
## Primary end-point

- 3 year Disease Free Survival
- FPI: Q4 2011
- Follow-up: 3 years (median)
- Expect filing 2016



# CLEOPATRA trial: Primary endpoint

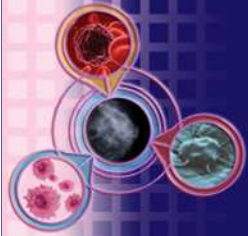
## Independently assessed PFS ( $n = 433$ PFS events)



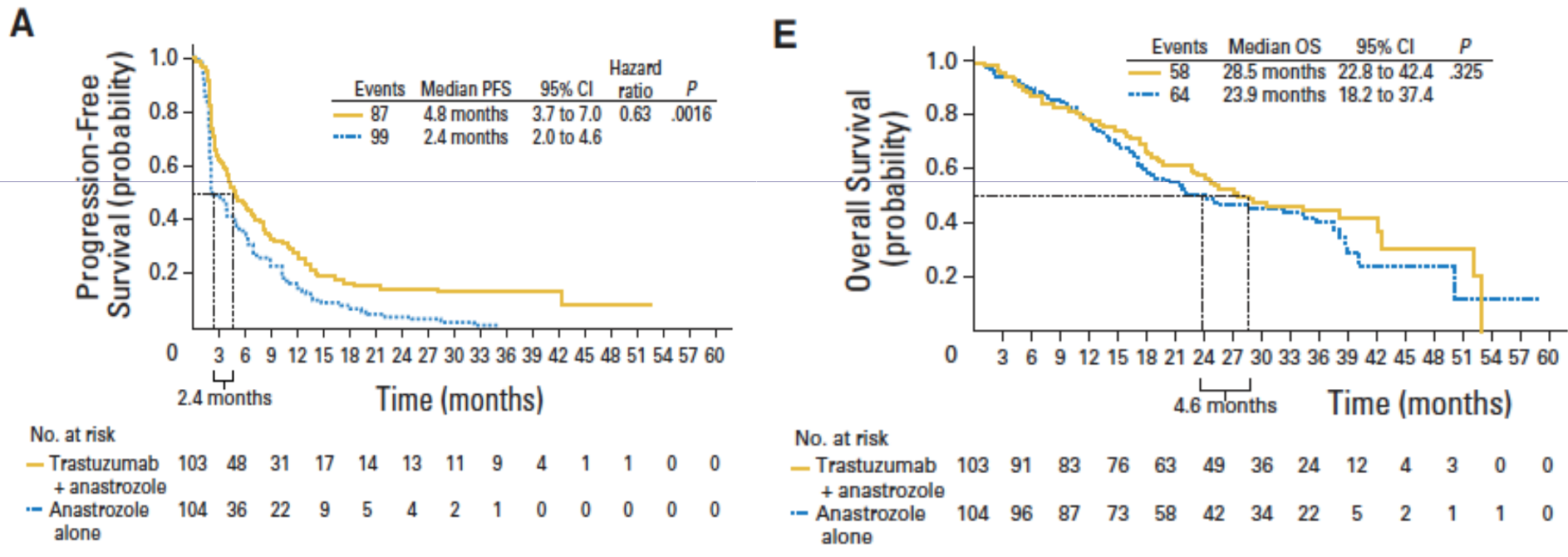
|                                     |             | n at risk |     |     |     |    |    |    |    |    |
|-------------------------------------|-------------|-----------|-----|-----|-----|----|----|----|----|----|
|                                     |             | 0         | 5   | 10  | 15  | 20 | 25 | 30 | 35 | 40 |
| <span style="color: red;">—</span>  | Ptz + T + D | 402       | 345 | 267 | 139 | 83 | 32 | 10 | 0  | 0  |
| <span style="color: blue;">—</span> | Pla + T + D | 406       | 311 | 209 | 93  | 42 | 17 | 7  | 0  | 0  |

D, docetaxel; PFS, progression-free survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Baselga et al, SABCS, 2011

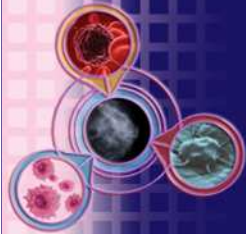


# TAnDEM study: Anastrozole +/- trastuzumab

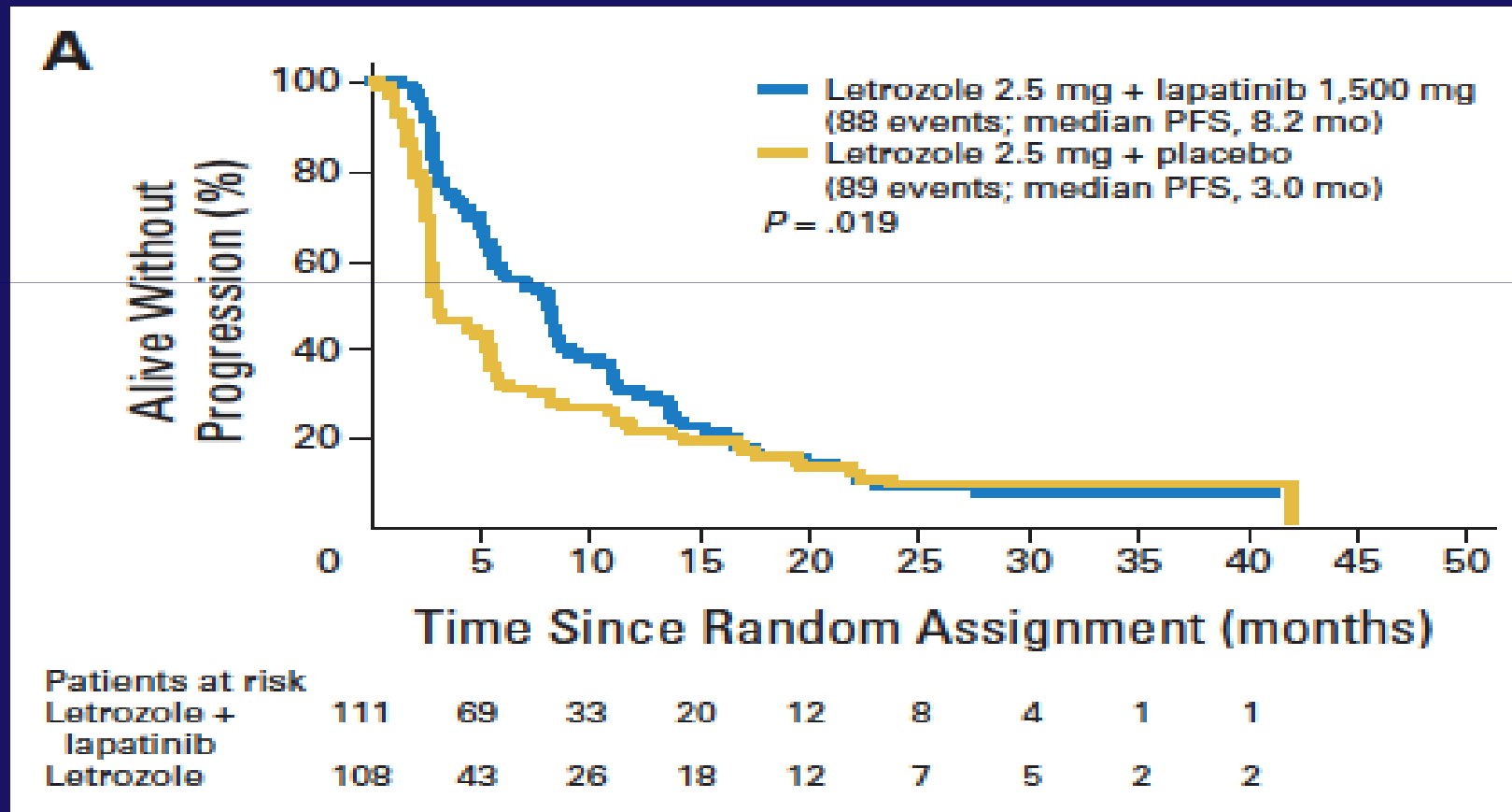


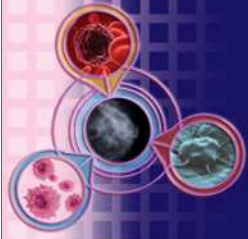
*Kaufman B, J Clin Oncol, 2009, 27:5529-5537*



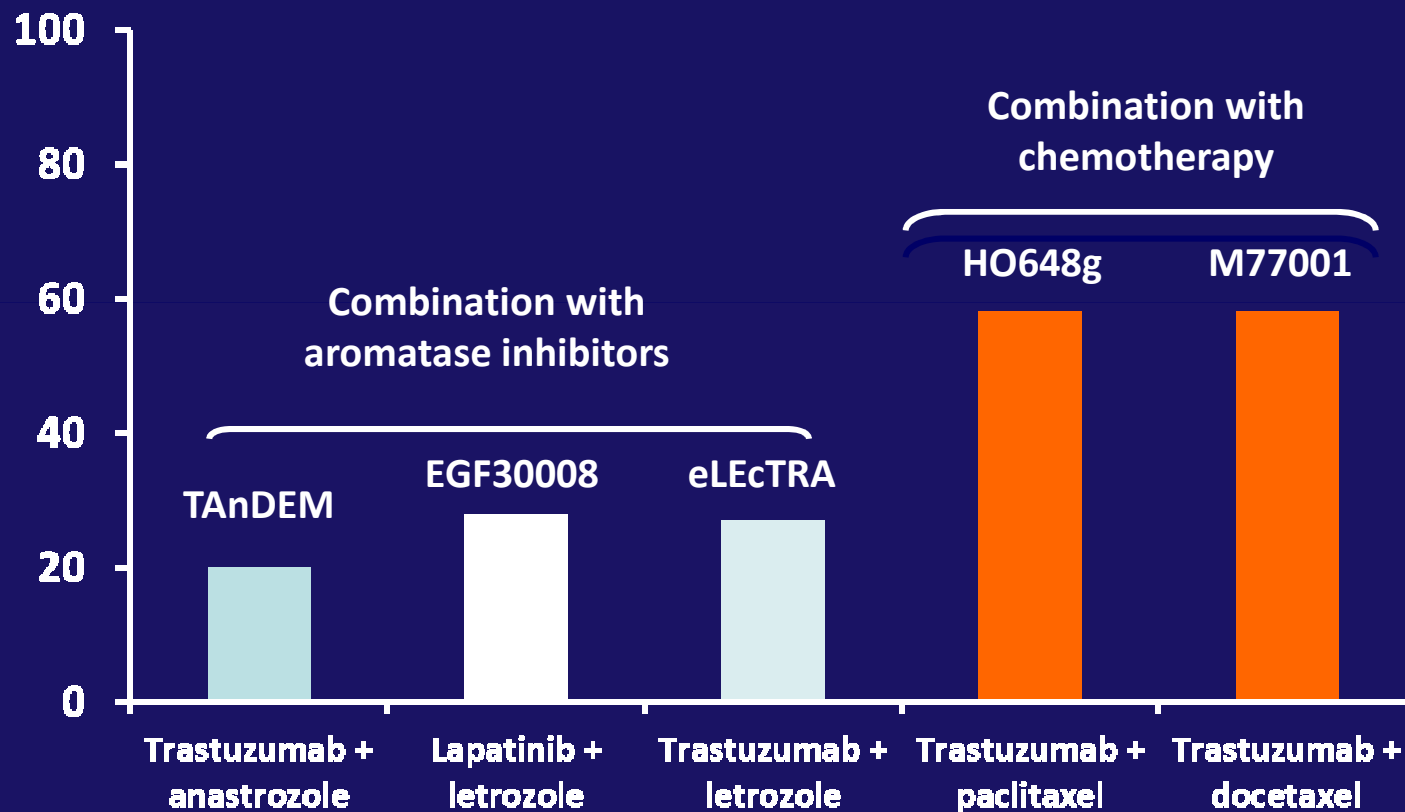


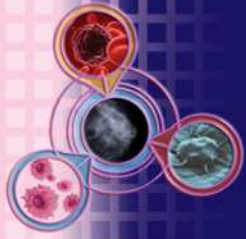
# EGF 30008: Letrozole +/- lapatinib





# HER2+/ ER+ metastatic breast cancer first-line treatment





# T-DM1: A HER2-Targeted Antibody-Drug Conjugate



**Humanized HER2 mAb: trastuzumab**

T-DM1 retains antitumor activities of trastuzumab



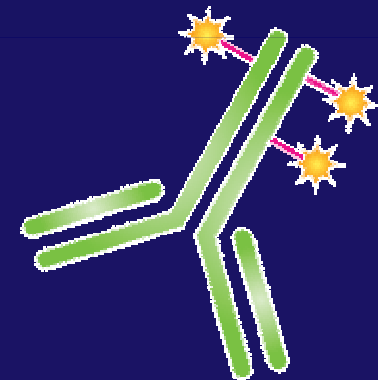
**Cytotoxic drug: DM1**

Potent cytotoxic agent  
(inhibitor of tubulin polymerization and  
microtubule dynamics)



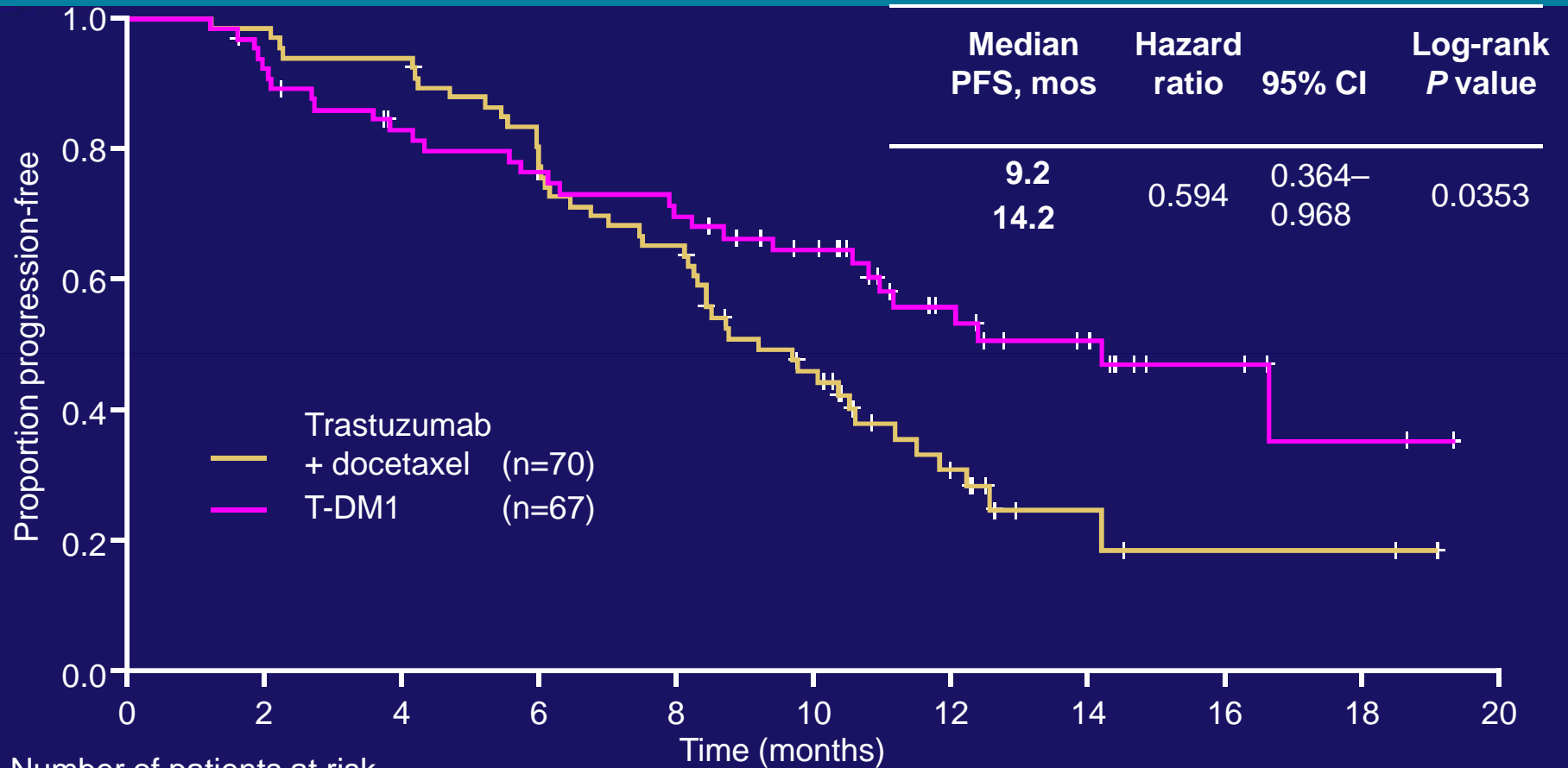
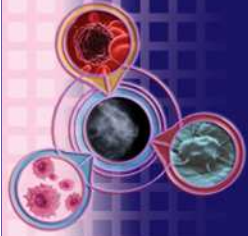
**Nonreducible thioether linker: SMCC**

Systemically stable



**T-DM1**

# Progression-Free Survival by Investigator

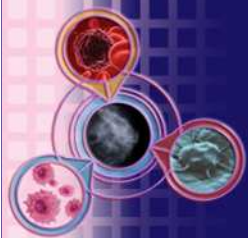


Number of patients at risk

|       |    |    |    |    |    |    |    |    |   |   |   |
|-------|----|----|----|----|----|----|----|----|---|---|---|
| T+D   | 70 | 66 | 63 | 53 | 43 | 27 | 12 | 4  | 2 | 2 | 0 |
| T-DM1 | 67 | 60 | 51 | 46 | 42 | 35 | 22 | 15 | 6 | 3 | 0 |

Hazard ratio and log-rank *P* value were from stratified analysis.

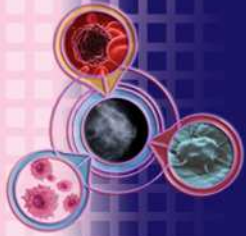
Hurwitz SA et al. ESMO 2011 Abstr 5001



# Adverse Event Summary

## Safety Evaluable Patients

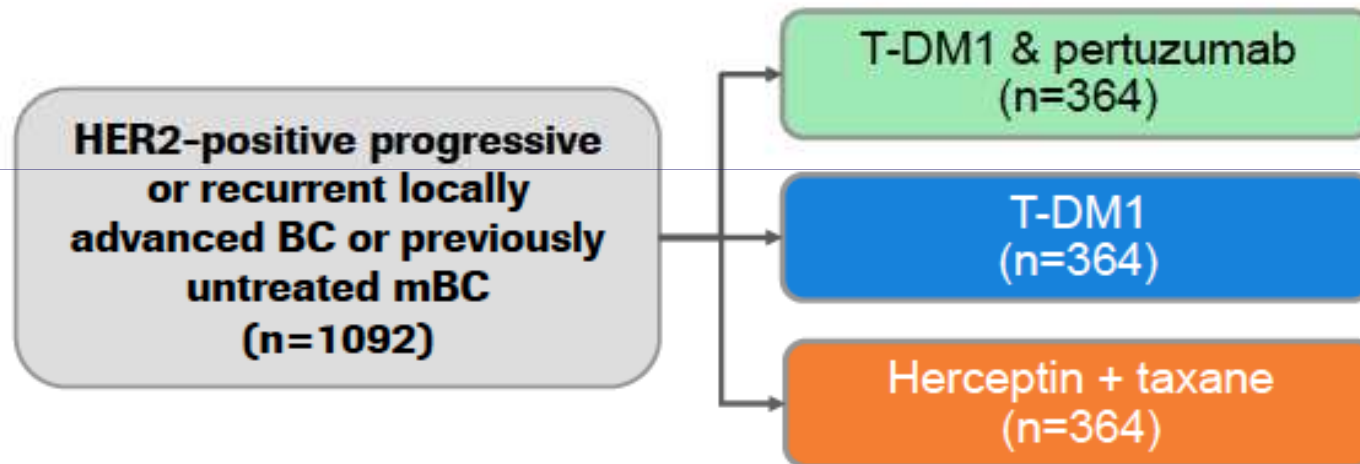
|   | T-DM1<br>(n=67)  | Trastuzumab+Docetaxel<br>(n=68) |
|---|------------------|---------------------------------|
| <b>Any AE, n (%)</b>  | 63 (94.0)        | 68 (100.0)                      |
| <b>Grade ≥3 AE</b>  | <b>25 (37.3)</b> | <b>51 (75.0)</b>                |
| <b>Serious AE*</b>  | 13 (19.4)        | 15 (22.1)                       |
| <b>Three most common AEs (any grade) in T-DM1 arm</b>                   |                  |                                 |
| Nausea  | 32 (47.8)        | 27 (39.7)                       |
| Fatigue   | 31 (46.3)        | 29 (46.2)                       |
| Pyrexia   | 24 (35.8)        | 14 (20.6)                       |
| <b>Three most common AEs (any grade) in trastuzumab + docetaxel arm</b> |                  |                                 |
| Alopecia  | 1 (1.5)          | 45 (66.2)                       |
| Neutropenia   | 5 (7.5)          | 39 (57.4)                       |
| Diarrhea  | 7 (10.4)         | 31 (45.6)                       |



# First-line HER2-positive mBC

## MARIANNE trial

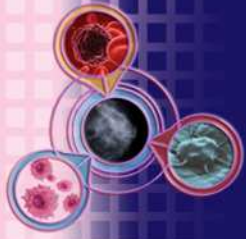
### *T-DM1 and pertuzumab vs. standard of care*



#### Primary end-point

- Progression-free survival
- Recruitment started Q3 2010
- Expect filing 2014

**Plan to file T-DM1 and T-DM1+pertuzumab in 1L HER2+ MBC with PFS superiority over Herceptin + taxane**



## Is there still a place for chemotherapy in the HER2 positive breast cancer?

**Chemotherapy should be given to all patients in the adjuvant setting**

**A high pCR rate is observed with dual HER2 blockade in the neoadjuvant setting. We don't have predictive factors allowing to identify patients who don't need chemotherapy**

**Chemotherapy is also indicated for endocrine sensitive tumors overexpressing HER2**