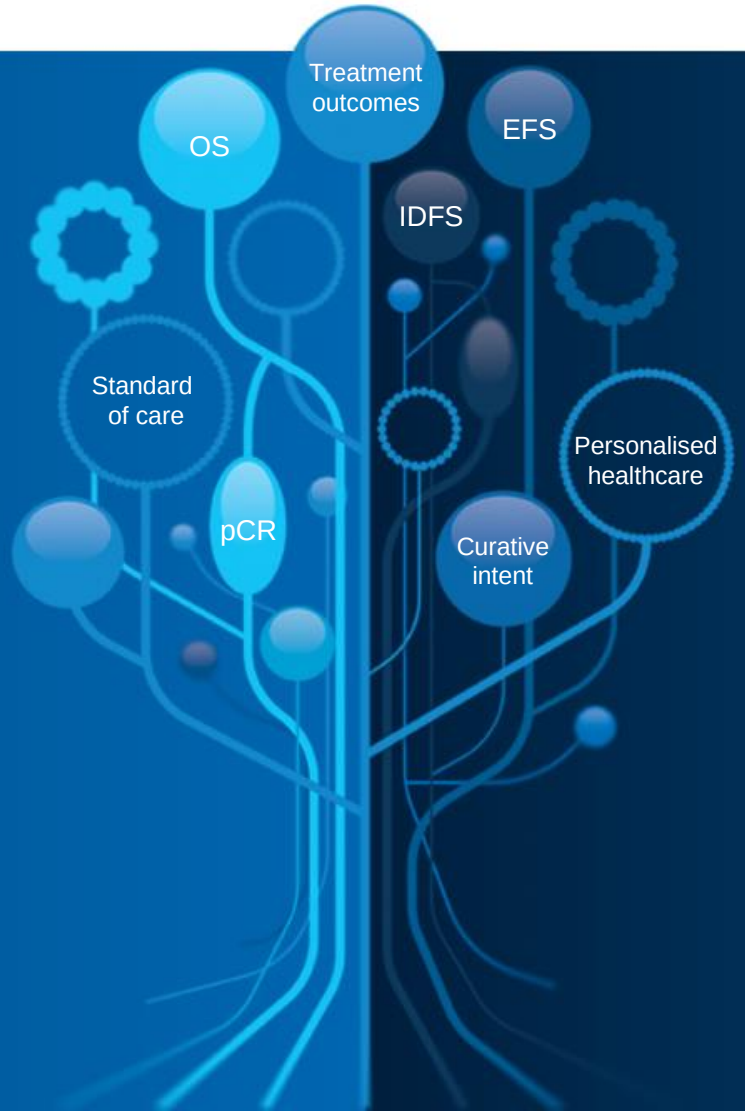
*Annual updates on Breast Cancer 2018*
*– from trial to clinical practice*




# Navigating HER2-positive early breast cancer treatment

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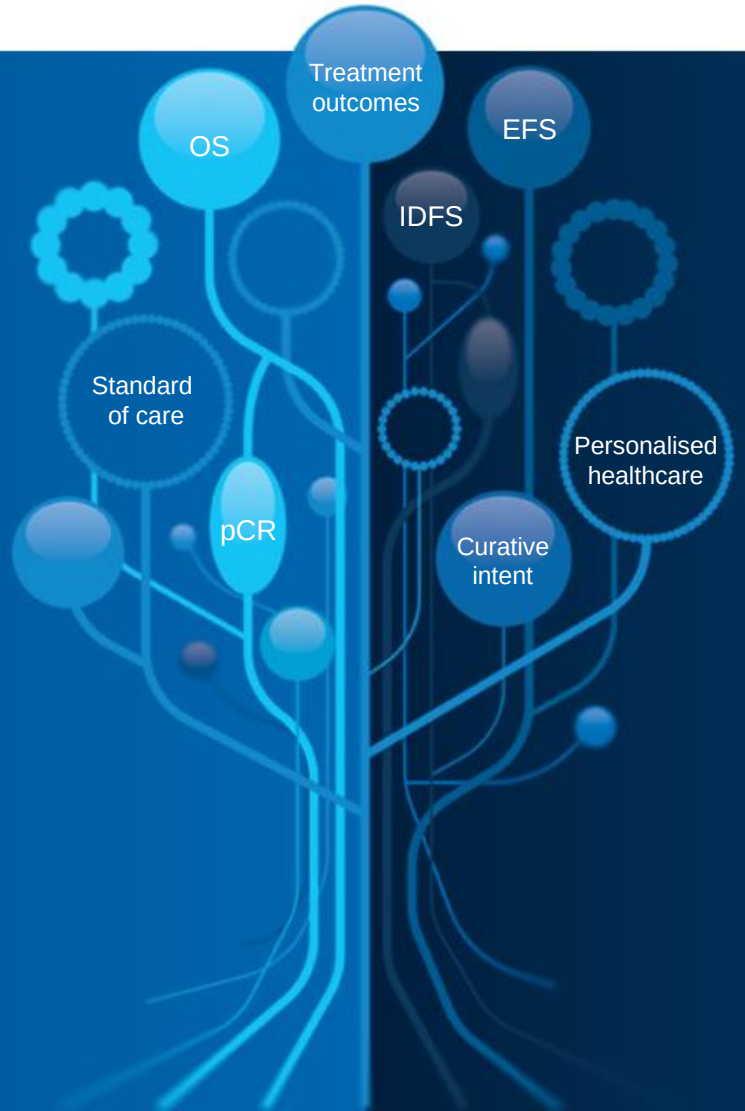
*Specialist in Clinical Oncology*

# Agenda

1. Current standard of care in early breast cancer (eBC)
2. Potential for treatment de-escalation in neoadjuvant setting
3. Need for treatment escalation with incorporation of newer modalities
4. Bridging neoadjuvant to adjuvant treatment




# Current standard of care in eBC

# Breast cancer cure rates are increasing, however…

**BC remains a leading cause of female cancer deaths[1,2]**

**~30% of patients treated for eBC go on to develop mBC[3]**

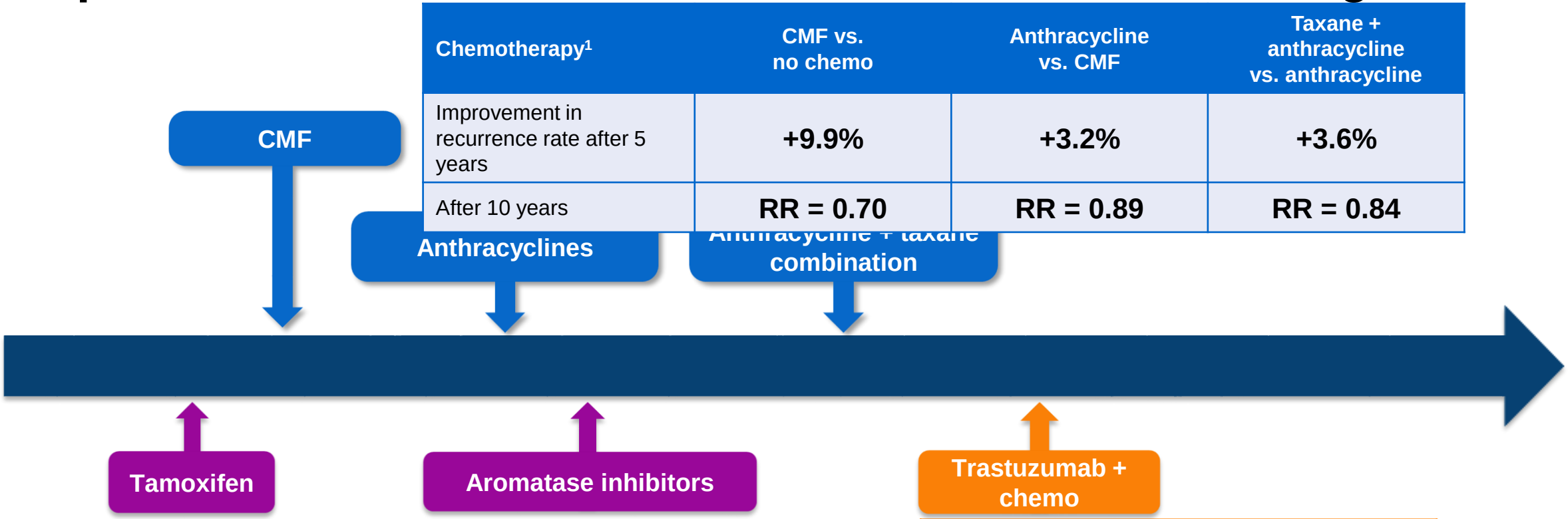
Treatment in **eBC has a curative intent**;[4] therefore, **patients should be given the most efficacious treatment available**

**mBC with distant organ metastases is considered essentially incurable.[5] It is important to treat patients with effective therapies as early as possible.**

1. Ferlay J, *et al*. *Int J Cancer* 2015; **136**:e359–e386; 2. GLOBOCAN database, http://globocan.iarc.fr/Default.aspx (accessed Sept 2016);
3. O'Shaughnessy J. *The Oncologist* 2005; **10 (suppl 3):**20–29; 4. Scharl A, *et al*. *Geburtshilfe Frauenheilkd* 2015; **75**:683–691;
5. Savci-Heijink CD *et al*. *Breast Cancer Treat* 2015; **150**:547–557.

# Introduction of new treatment modalities over time has improved recurrence outcomes in the ADJUVANT setting

| Chemotherapy[1] | CMF vs. no chemo | Anthracycline vs. CMF | Taxane + anthracycline vs. anthracycline |
|---|---|---|---|
| Improvement in recurrence rate after 5 years | +9.9% | +3.2% | +3.6% |
| After 10 years | RR = 0.70 | RR = 0.89 | RR = 0.84 |



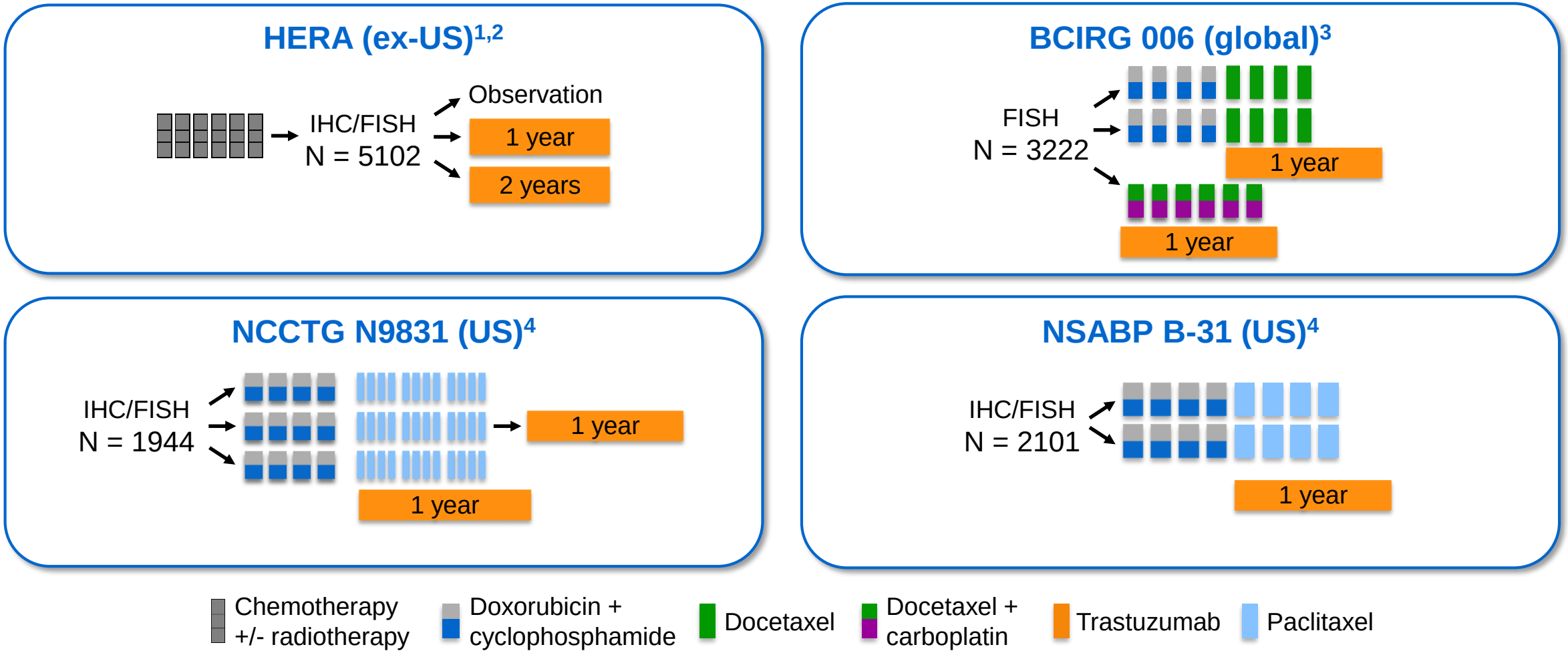

| Endocrine therapy[2,3] | Tam 5 years vs. no tam | AI 5 years vs. tam 5 years |
|---|---|---|
| Improvement in recurrence rate after 5 years | +11.4% | +3.1% |
| After 5 years | RR = 0.69 | RR = 0.80 |

| Anti-HER2 therapy[4–6] | Trastuzumab vs. chemo/observation |
|---|---|
| DFS benefit after 10 years | +5.1-6.8% |
| After 10/11 years | (HR = 0.72–0.77) |

AI, aromatase inhibitor; CMF, cyclophosphamide, methotrexate and fluorouracil; HR, hazard ratio; RR, risk ratio.


1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet* 2012; **379**:432–444; 2. EBCTCG. *Lancet* 2015; **386**:1341–1352; 3. EBCTCG. *Lancet* 2005; **365**:1687–1717; 4. Jackisch C, *et al*. SABCS 2015; Poster PD5-01; 5. Slamon D, *et al*. SABCS 2015; Oral presentation S5-04; 6. Slamon D, *et al. N Engl J Med* 2011; **365**:1273–1283.

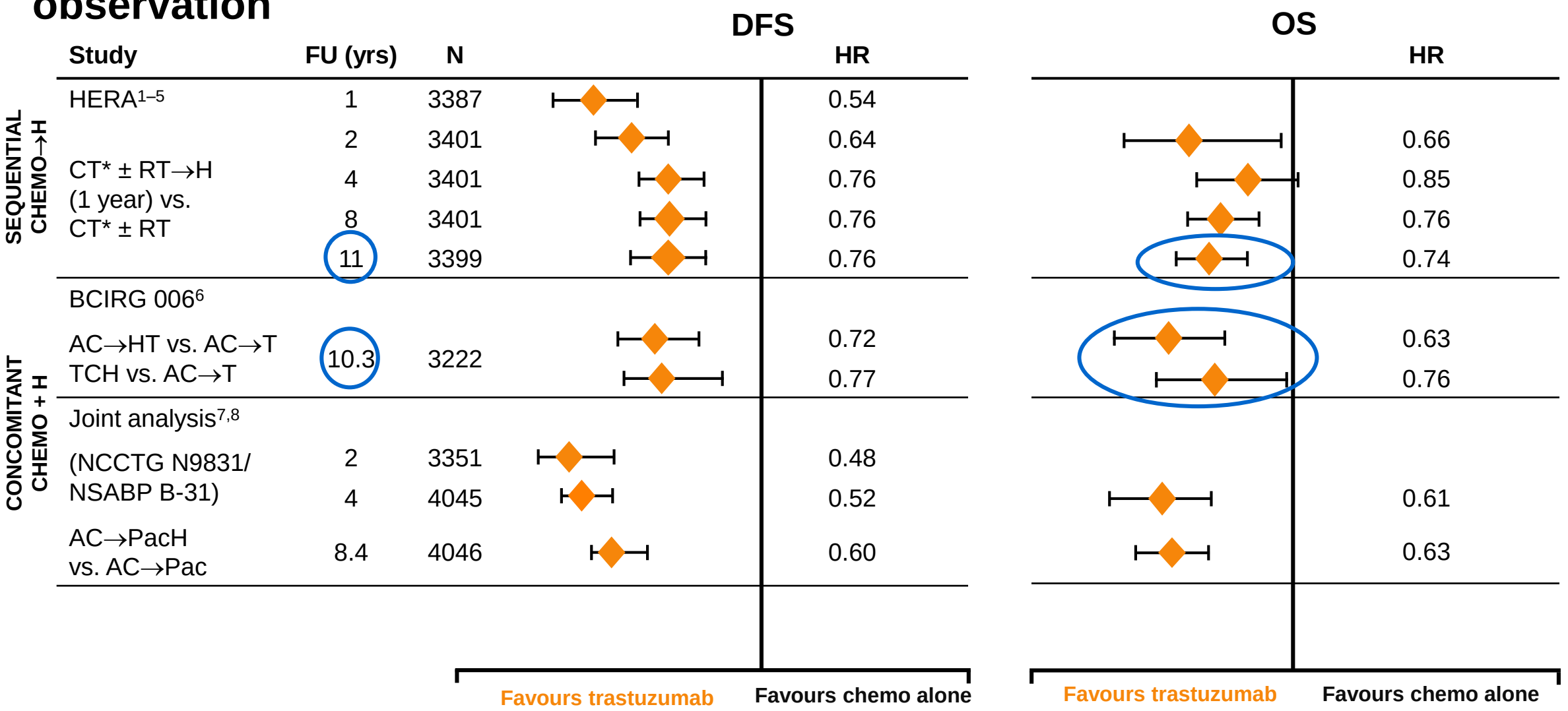
# Four pivotal trials (>12,000 patients) established 18 cycles (1 year) of adjuvant trastuzumab as the SoC for HER2-positive eBC




IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridisation.

1. Piccart-Gebhart MJ, *et al. N Engl J Med* 2005; **353**:1659–1672; 2. Gianni L, *et al. Lancet Oncol* 2011; **12**:236-244; 3. Slamon D, *et al. N Engl J Med* 2011; **365**:1273–1283; 4. Perez EA, *et al. J Clin Oncol* 2011; **29**:3366–3373.

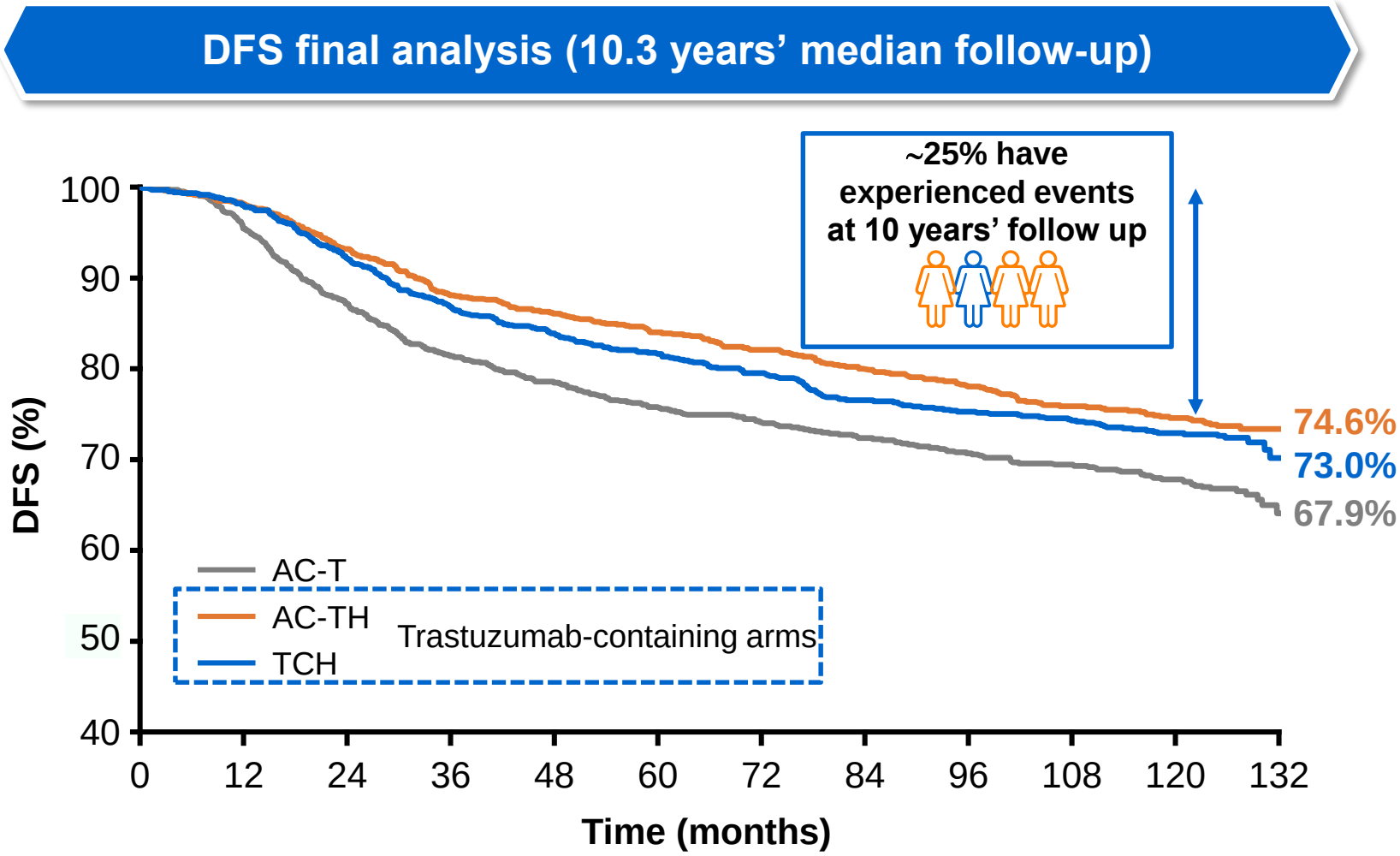
# These adjuvant trials demonstrated consistent DFS and OS benefit over time with 1 year of trastuzumab treatment vs. observation




AC, doxorubicin + cyclophosphamide; C, carboplatin; CT, chemotherapy; DFS, disease-free survival; FU, follow-up; H, trastuzumab; OS, overall survival; Pac, paclitaxel; RT, radiotherapy; T, docetaxel.
* Selected from a list of approved regimens consisting of ≥4 cycles.


1. Piccart-Gebhart MJ, *et al*. *N Engl J Med* 2005; **353**:1659–1672; 2. Smith I, *et al*. *Lancet* 2007; **369**:29–36; 3. Gianni L, *et al*. *Lancet Oncol* 2011; **12**:236–244; 4. Goldhirsch A, *et al*. *Lancet* 2013; **382**:1021–1028; 5. Cameron D, *et al*. *Lancet* 2017; **389**:1195–1205; 6. Slamon D, *et al*. SABCS 2015 (Abstract S5-04; oral presentation); 7. Perez EA, *et al*. *J Clin Oncol* 2011; **29**:3366–3373; 8. Perez EA, *et al*. *J Clin Oncol* 2014; **32**:3744–3752; .

# BCIRG 006: Relapse rates in HER2-positive eBC remain high despite the significant impact of trastuzumab-based therapy

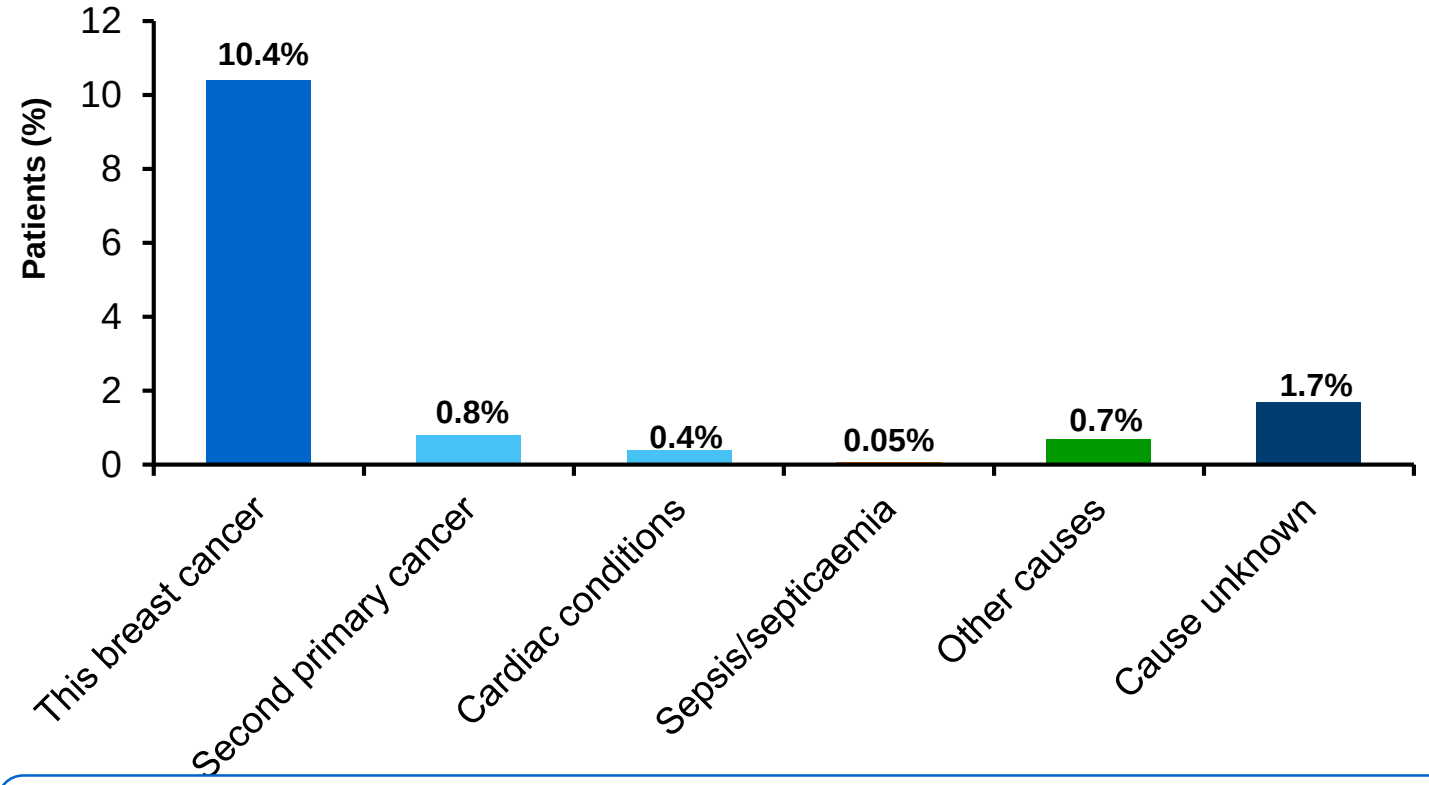



**1 in 4 patients will still experience recurrence or death**
despite 1 year of adjuvant trastuzumab-based therapy

Slamon D, *et al*. SABCS 2015 (Abstract S5-04; oral presentation).

# The majority of deaths following adjuvant trastuzumab are from recurrence of BC

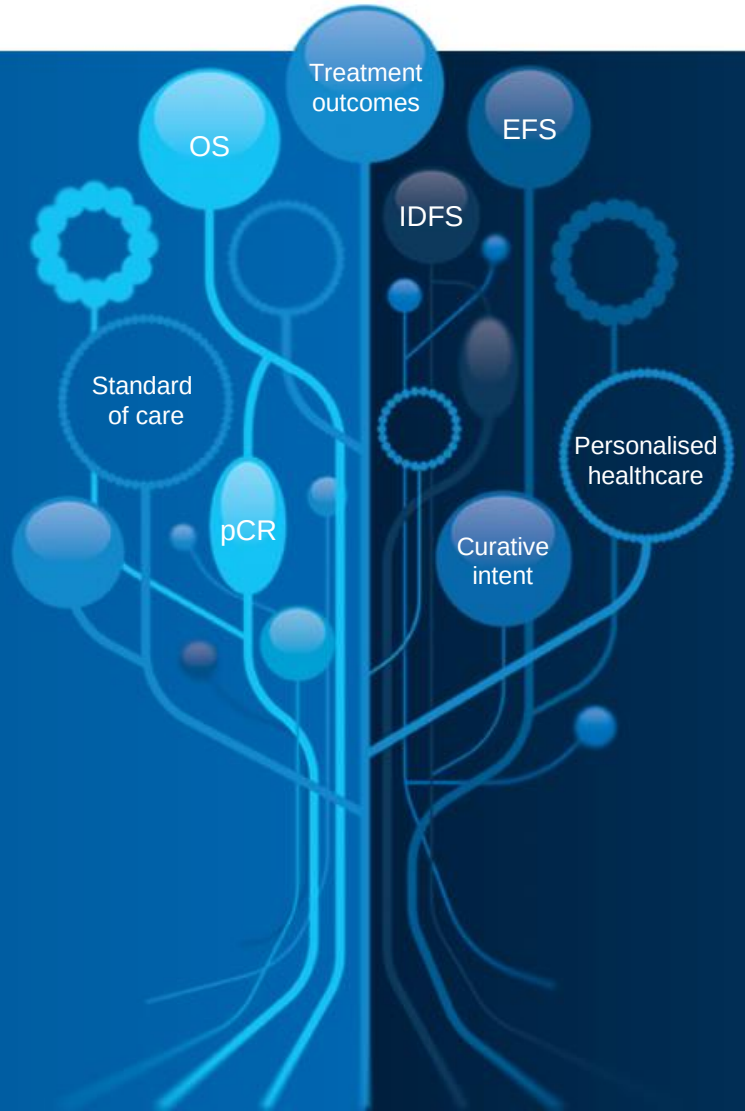
**B-31/N9831: 10-year overall survival events and causes of death in patients treated with trastuzumab**




**BC was the cause of death for the majority of the ~14% of patients who died**

**Although trastuzumab has revolutionised treatment of women with HER2-positive BC, many patients still die from disease recurrence**

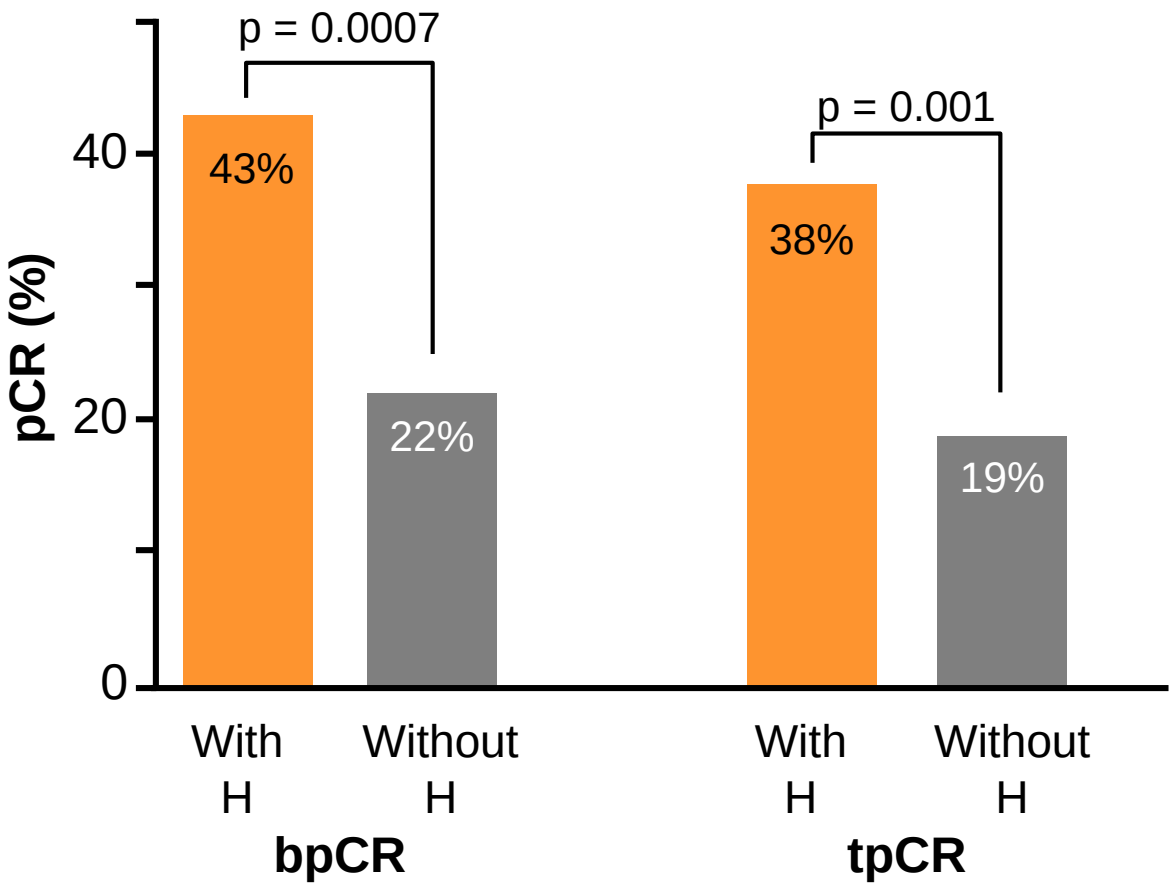
Perez EA, *et al. J Clin Oncol* 2014; **32**:3744–3752.

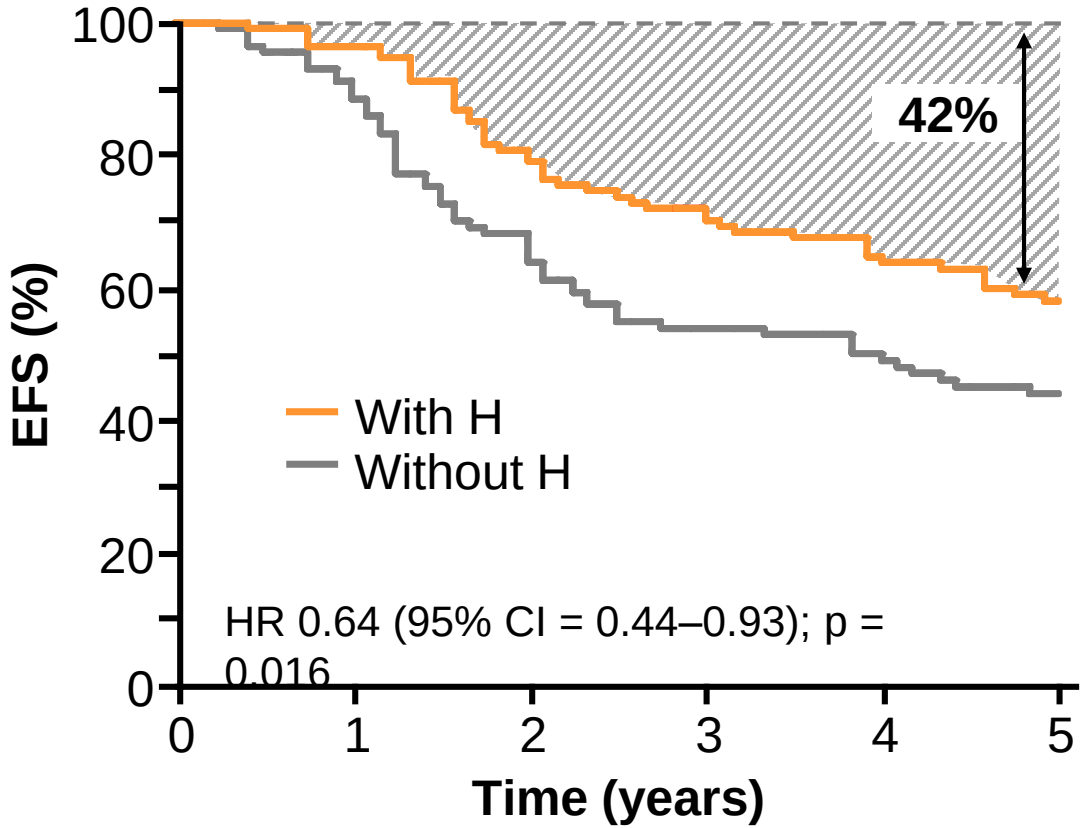



# What have we learnt from dual inhibition in neoadjuvant setting?

# NOAH: Trastuzumab increased both pCR and EFS, but many patients still experience relapse

**Increased pCR rates with trastuzumab added to chemotherapy resulted in improved EFS, but 42% of patients had relapsed at 5 years**

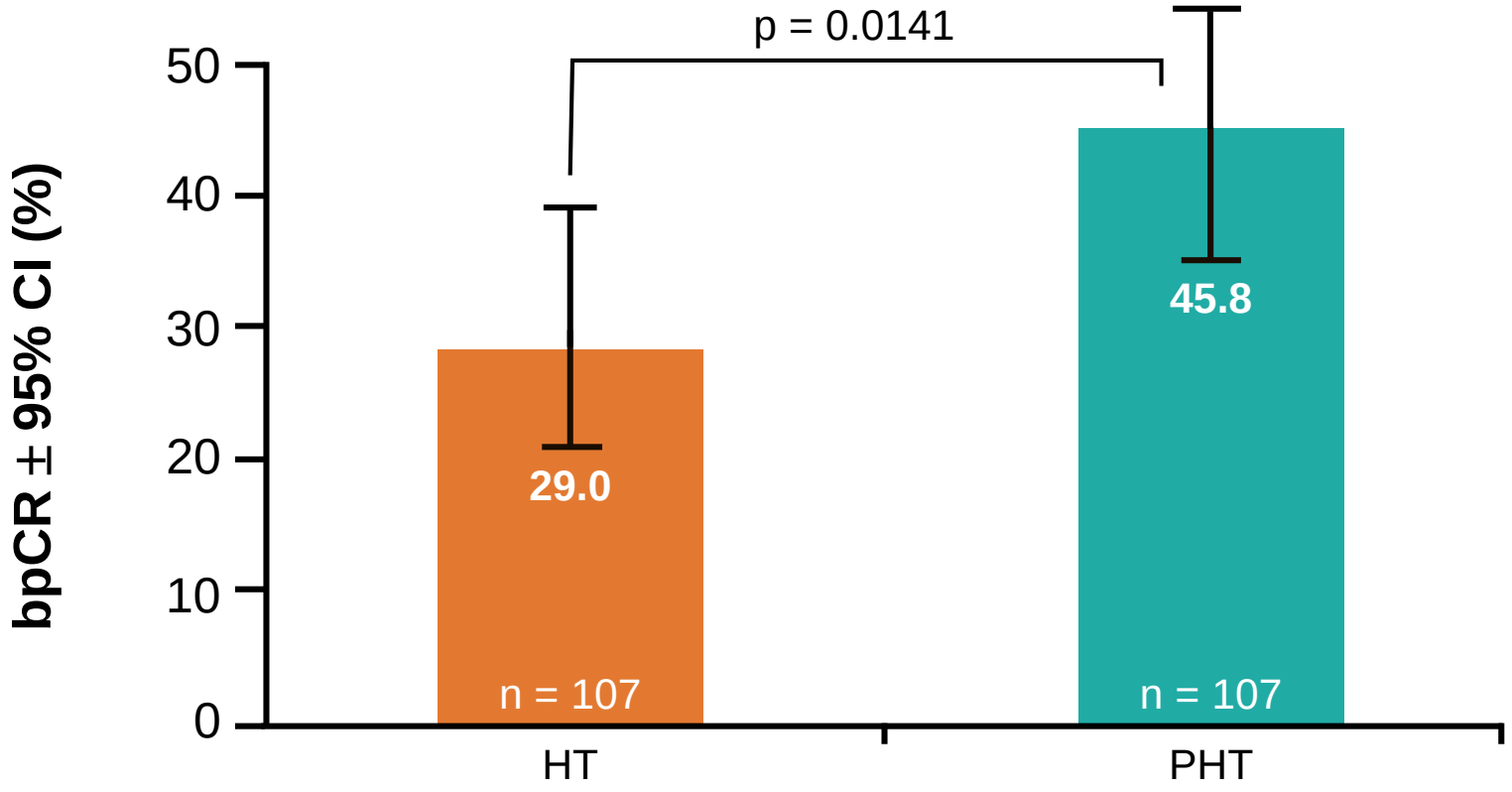



Gianni L, *et al. Lancet* 2010; **375**:377–384; Gianni L, *et al. Lancet Oncol* 2014; **15**:640–647.

# NeoSphere: Dual HER2 targeting with pertuzumab–trastuzumab was associated with improved pCR

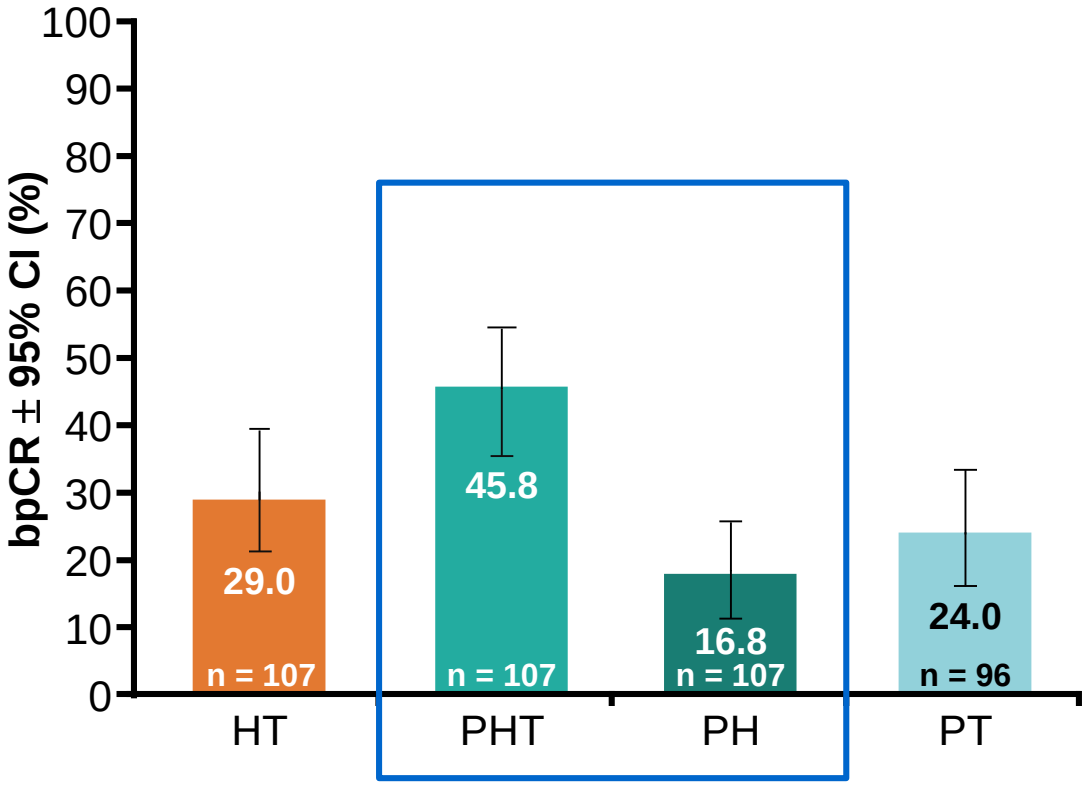
**Pertuzumab–trastuzumab plus docetaxel significantly increased pCR rates vs. trastuzumab plus docetaxel alone, leading to pertuzumab approval**



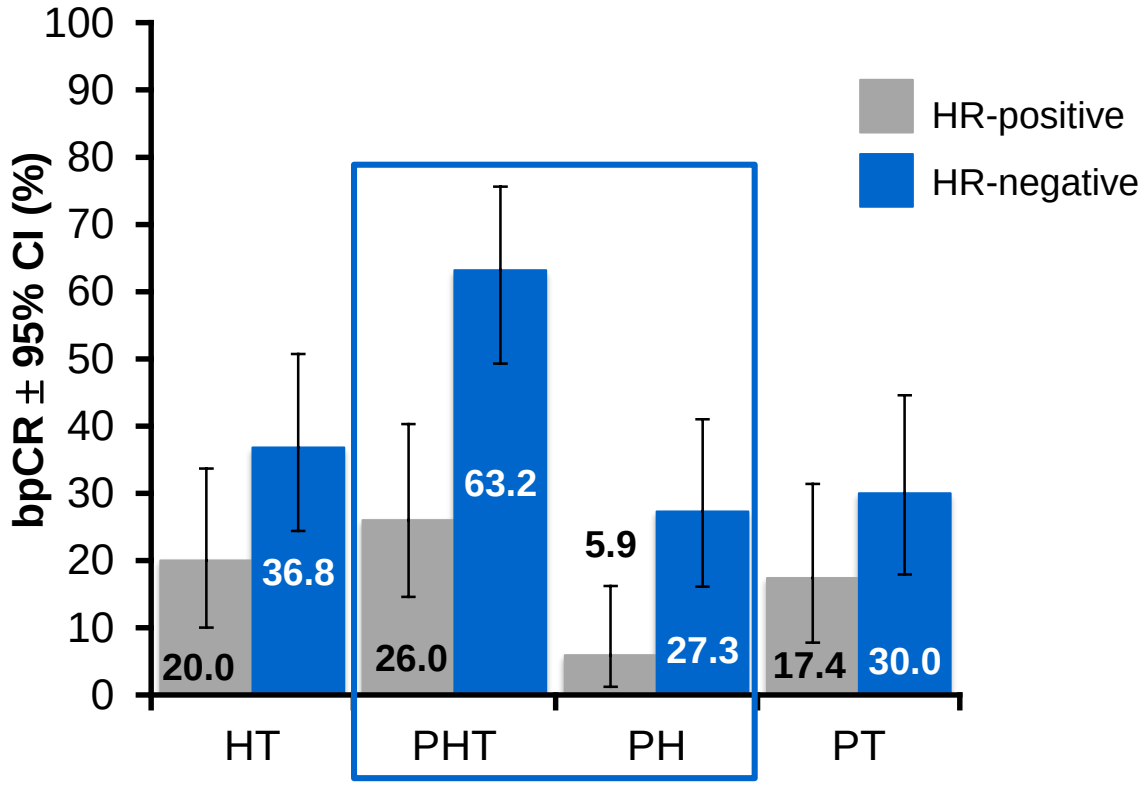

Gianni L, *et al. Lancet Oncol* 2012; **13**:25–32; Gianni L, *et al. Lancet Oncol* 2016; **17**:791–800.

# NeoSphere: PHT improved pCR regardless of HR status; however, HR-negative disease appears more reliant on the HER2-signalling pathway

## pCR in the breast*




## pCR in the breast by HR status*

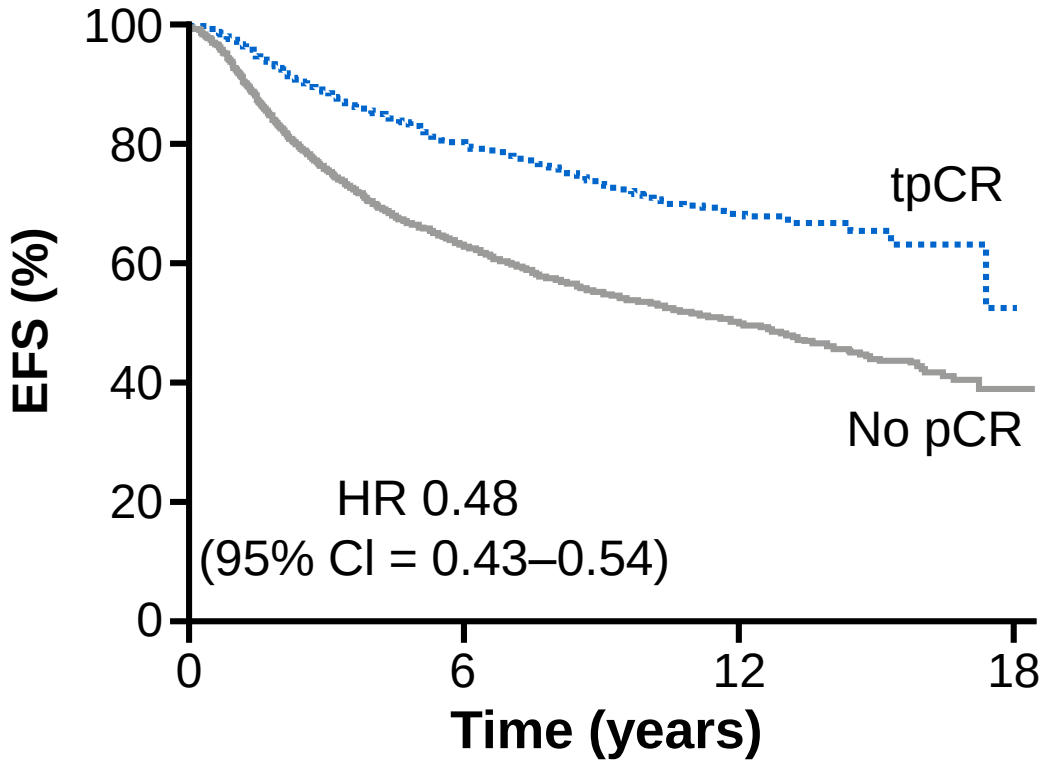



bpCR, pathological complete response in the breast;
CI, confidence interval; P, pertuzumab; pCR, pathological complete response.
* NeoSphere: chemotherapy was given following surgery.

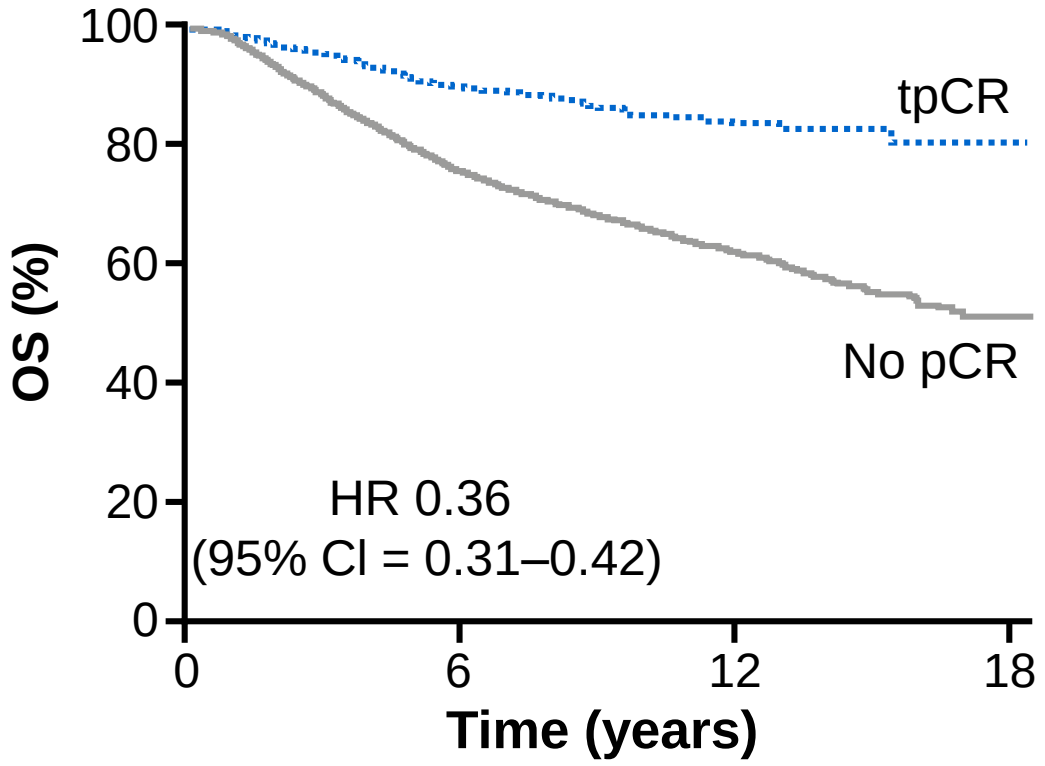
Gianni L, *et al*. *Lancet Oncol* 2012; **13**:25–32.

# CTNeoBC meta-analysis: Achieving a tpCR with neoadjuvant chemotherapy resulted in longer EFS and OS than not achieving a tpCR

## EFS




## OS

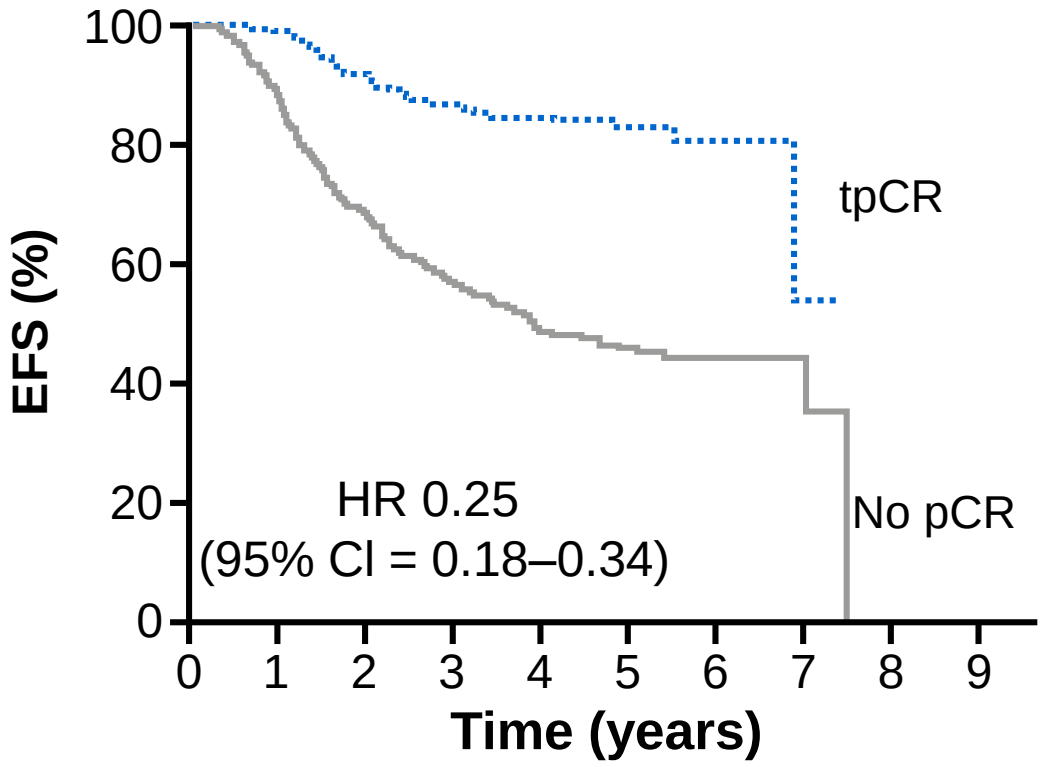



EFS, event-free survival.

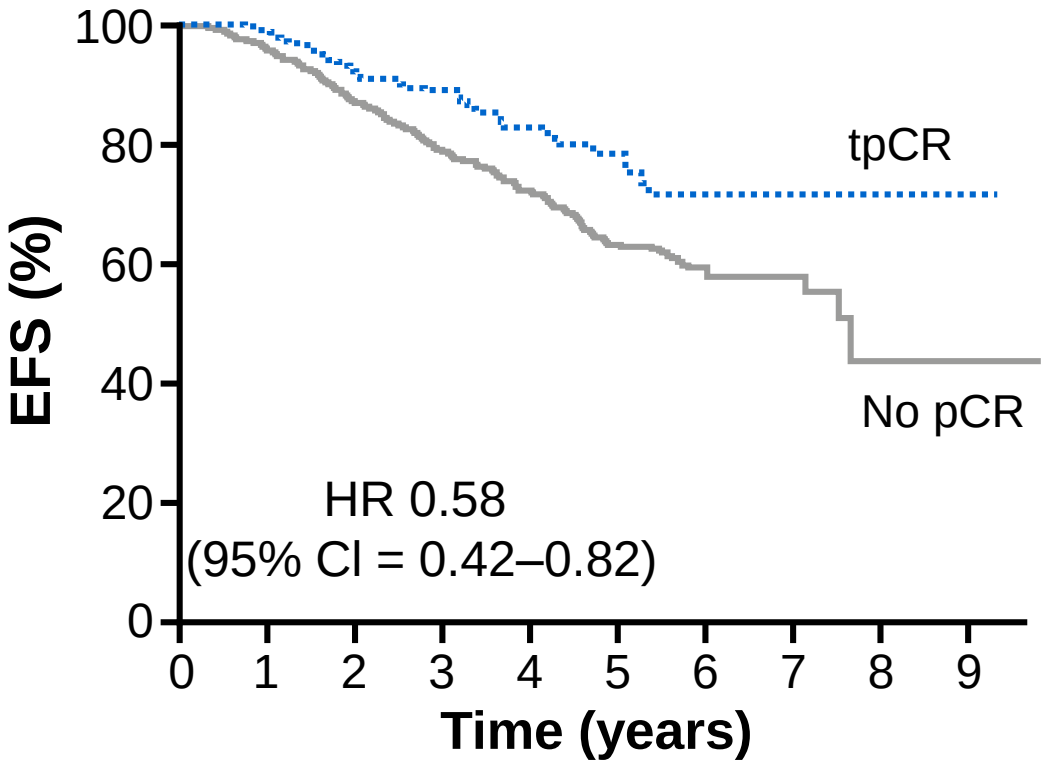
Cortazar P, *et al*. *Lancet* 2014; **384**:164–172.

# CTNeoBC meta-analysis: EFS benefit after pCR was more pronounced in HER2-positive, HR-negative tumours

## HER2-positive, HR-negative

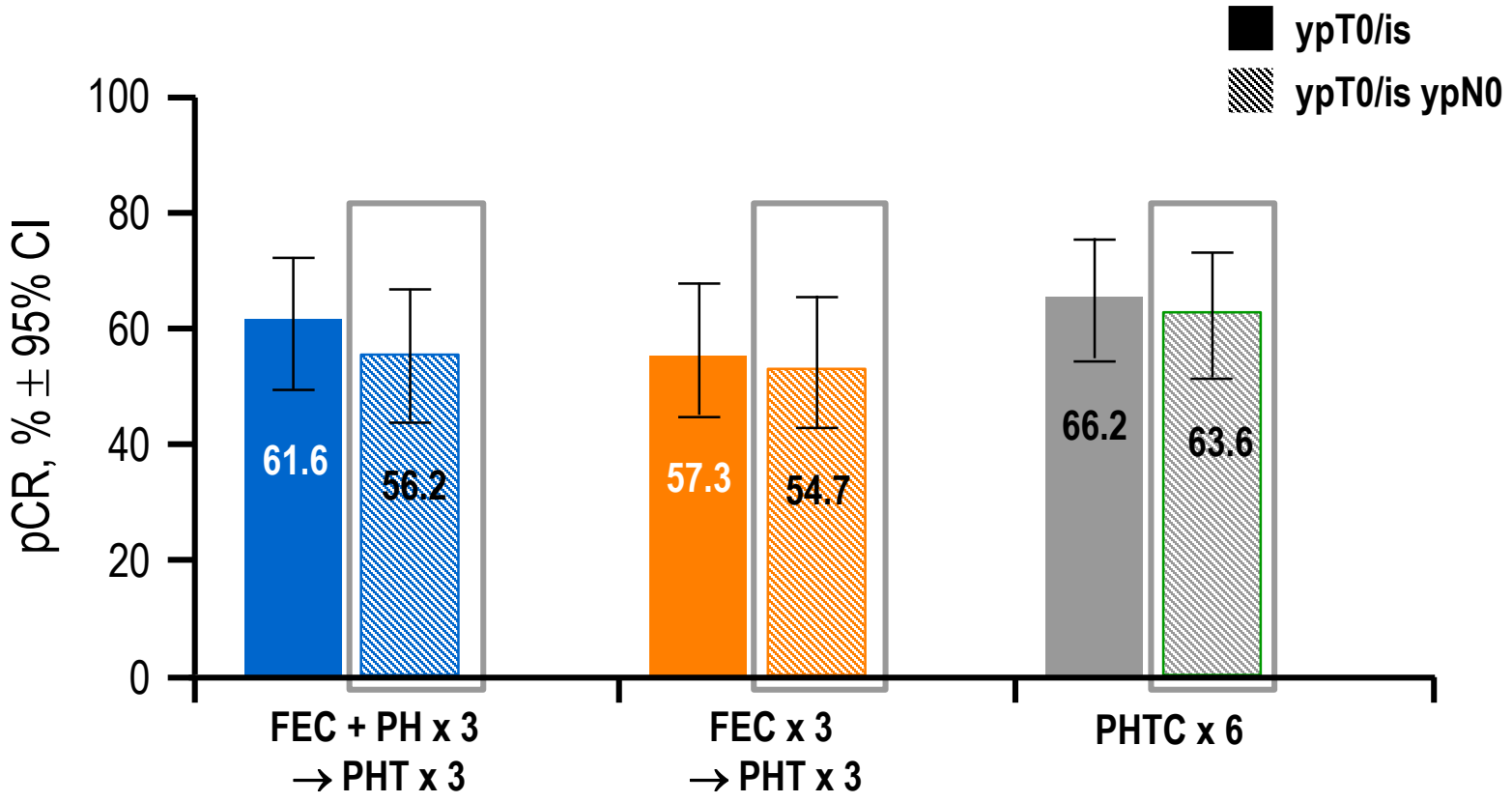



## HER2-positive, HR-positive



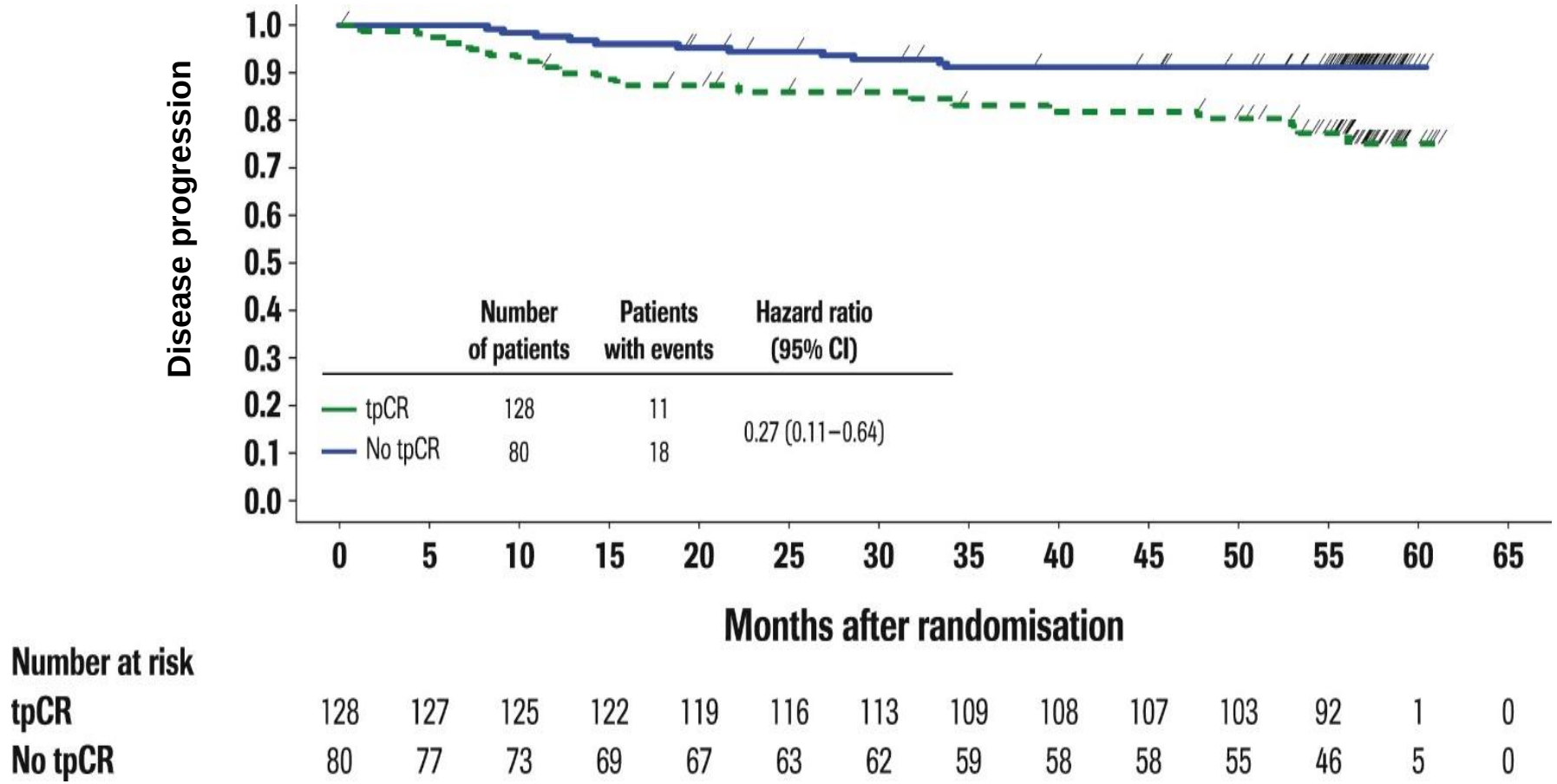

Cortazar P, *et al*. *Lancet* 2014; **384**:164–172.

# TRYPHAENA: The combination of pertuzumab and trastuzumab in the neoadjuvant setting resulted in high pCR rates, regardless of chemotherapy partner



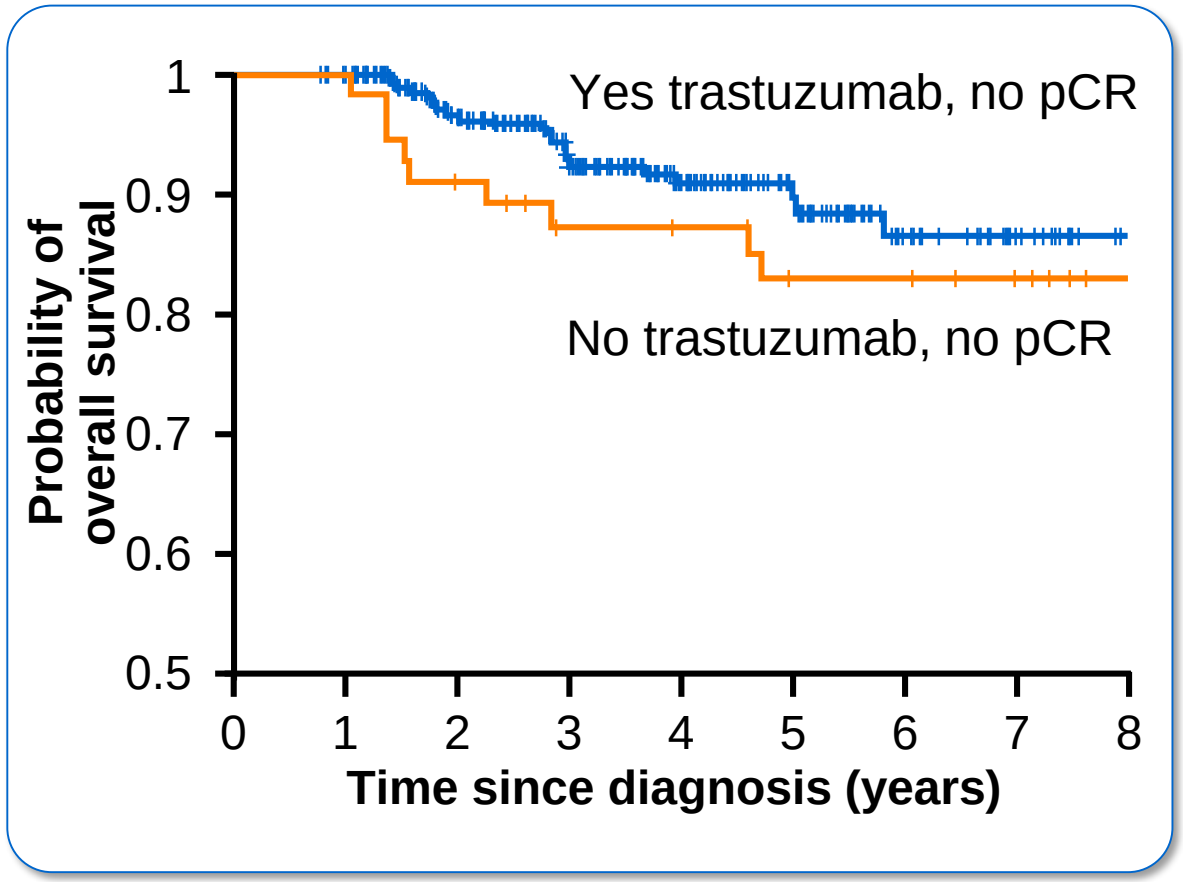

Schneeweiss, et al. Ann Oncol 2013

# TRYPHAENA 3-year follow-up: tpCR was associated with improved disease-free survival (DFS)




Schneeweiss A et al. European Journal of Cancer 2018; 89: 27-35.

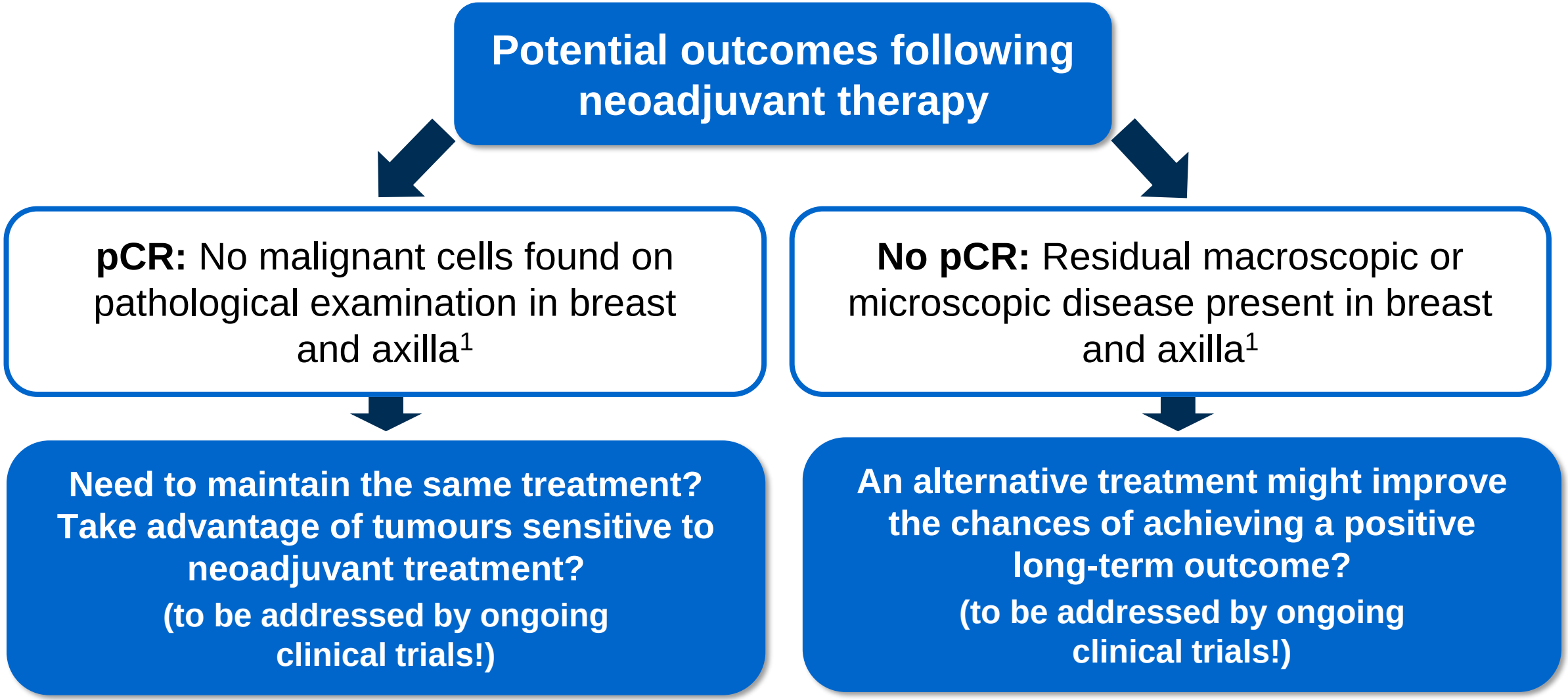
# Continuation of trastuzumab in non-pCR patients




**In a retrospective analysis, patients with HER2-positive eBC who did not achieve a pCR with neoadjuvant trastuzumab-based therapy appeared to benefit more from adjuvant trastuzumab (N = 589)**

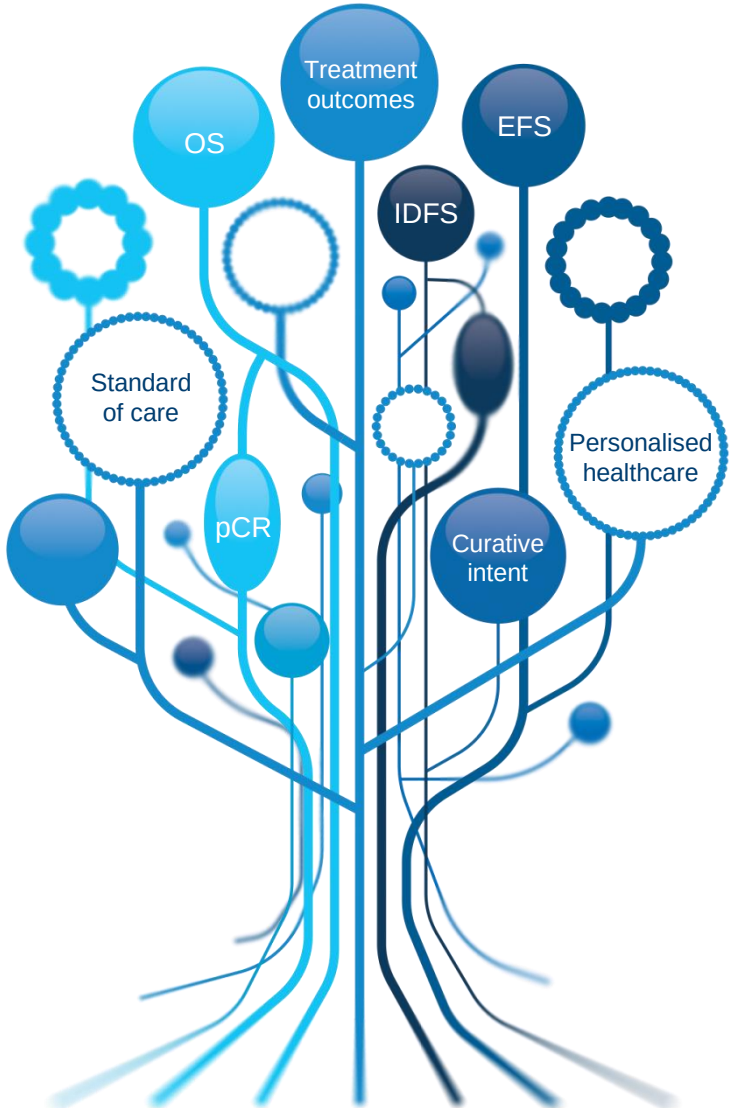
Gonzalez-Angulo AM, *et al*. *Br J Cancer* 2015; **112**:630–635.

# The outcome of neoadjuvant therapy may still influence subsequent treatment decisions




pCR, pathologic complete response.

1. FDA Guidance for Industry. https://www.fda.gov/downloads/drugs/guidances/ucm305501.pdf.




# Potential for treatment de-escalation

## *Omitting systemic chemotherapy in neoadjuvant setting?*

# Pathologic complete response rates after neoadjuvant trastuzumab emtansine (T-DM1) + pertuzumab vs docetaxel + carboplatin + trastuzumab + pertuzumab (TCH+P) treatment in patients with HER2-positive early breast cancer (KRISTINE/TRIO-021)

Sara A. Hurvitz,[1] Miguel Martin,[2] W. Fraser Symmans,[3] Kyung Hae Jung,[4] Chiun-Sheng Huang,[5] Alastair M.Thompson,[3] Nadia Harbeck,[6] Vicente Valero,[3] Daniil Stroyakovskiy,[7] Hans Wildiers,[8] Karen Afenjar,[9] Rodrigo Fresco,[10] Hans-Joachim Helms,[11] Jin Xu,[12] Yvonne G. Lin,[12] Joseph Sparano,[13] Dennis Slamon[1]

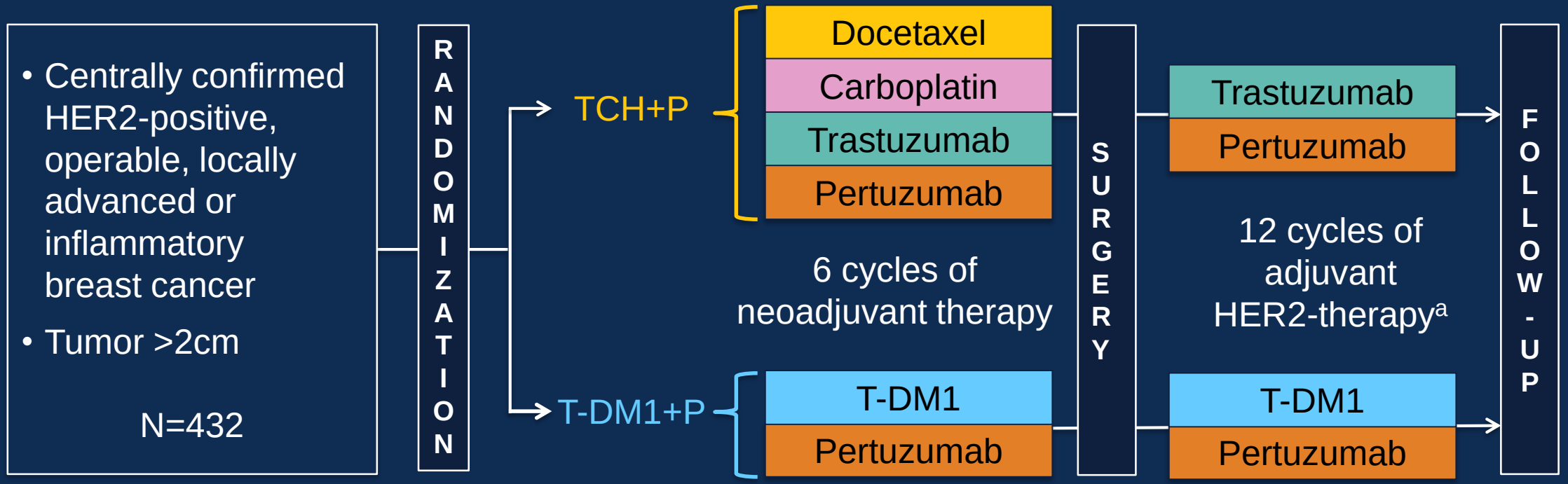
[1]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; [2]Hospital Gregorio Marañón, Universidad Complutense, Madrid, Spain; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [5]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; [6]Breast Center, University of Munich (LMU), Munich, Germany; [7]Moscow City Oncology Hospital, Stepanovskoye, Moscow, Russia; [8]University Hospitals Leuven, Leuven, Belgium; [9]Translational Research in Oncology, Paris, France; [10]Translational Research in Oncology, Montevideo, Uruguay; [11]F. Hoffmann-La Roche Ltd., Basel, Switzerland; [12]Genentech, Inc., South San Francisco, CA, USA; [13]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

PRESENTED AT: ASCO ANNUAL MEETING '16



Presented by: Dr Sara Hurvitz

# KRISTINE Study Design




**<u>Primary endpoint</u>: pCR by local assessment (ypT0/is, ypN0)**

- **Stratification factors:** local HR status, geographic location, and clinical stage at presentation

[a]Adjuvant chemotherapy was recommended for patients in the T-DM1+P arm who had residual disease in lymph node(s) or in the breast (>1cm).

# Patient Disposition

- Study conducted globally: 68 centers, 10 countries
- Total of 444 patients randomized from June 25, 2014 to June 15, 2015
- Clinical cut-off date: December 3, 2015

| | TCH+P | T-DM1+P |
|---|---|---|
| Randomized (ITT)[a], n | 221 | 223 |
| Treated (safety population), n | 219 | 223 |
| Median duration of follow-up including adjuvant phase, months (min–max) | 8.9 (0.1–15.7) | 8.8 (4.5–17.3) |

[a]Two patients randomized to the TCH+P arm did not receive any study drug (reasons for study discontinuation were: withdrawal by subject and other).
ITT, intent-to-treat.

# Demographics and Baseline Characteristics

| Characteristics | TCH+P (n=221) | T-DM1+P (n=223) |
|---|---|---|
| **Median age, years (min–max)** | 49 (22–79) | 50 (23–79) |
| **World region, %** | | |
| North America | 24 | 24 |
| Western Europe | 38 | 38 |
| Rest of the world | 38 | 38 |
| **Local ER/PR status, %** | | |
| ER and PR negative | 38 | 38 |
| ER and/or PR positive | 62 | 62 |
| **Clinical stage at presentation, %** | | |
| IIA–IIIA | 83 | 83 |
| IIIB–IIIC | 17 | 17 |

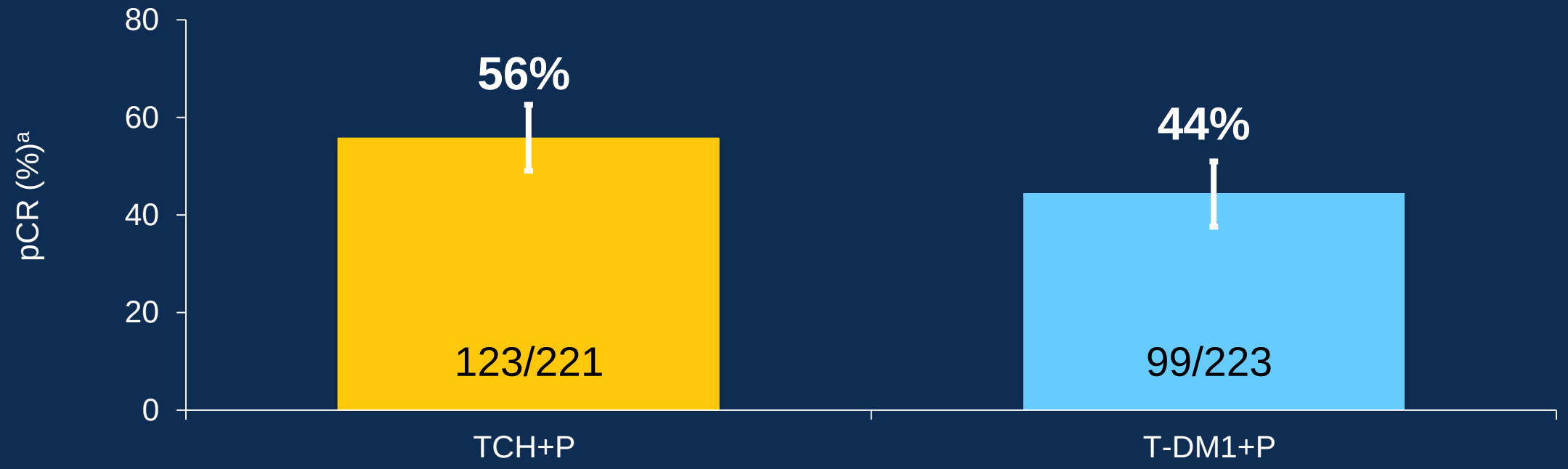
ER, estrogen receptor; PR, progesterone receptor.

# Primary Endpoint: pCR (ypT0/is, ypN0)

**Difference: -11.3**

95% CI: -20.5, -2.0

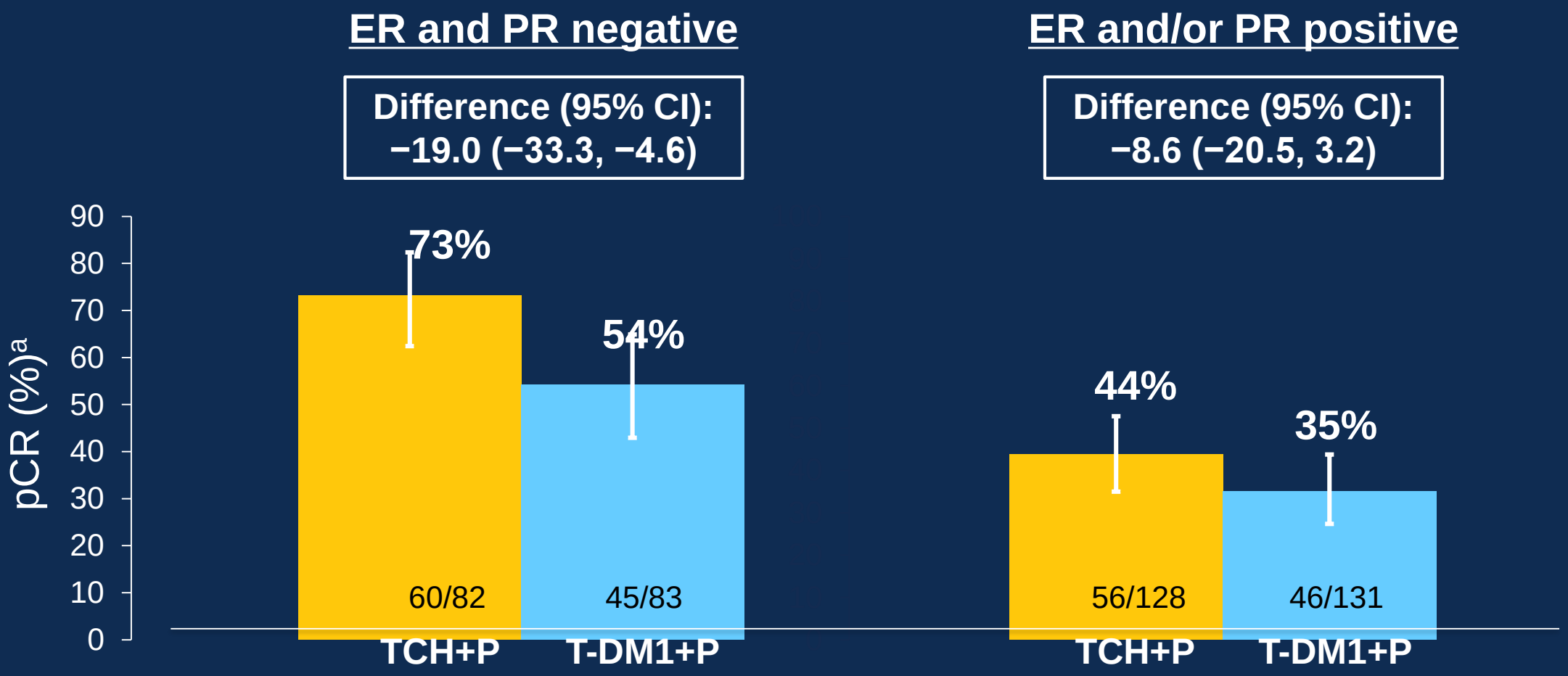
Stratified 2-sided *P*−value: 0.0155[b]




[a]pCR rate and 95% CI are shown. Patients with missing or unevaluable pCR status were considered nonresponders: TCH+P, 7 (3.2%); T-DM1+P, 18 (8.1%). Treatment discontinuation in the neoadjuvant phase for progressive disease: TCH+P, 0% of patients; T-DM1+P, 7% of patients.

[b]Cochran-Mantel-Haenszel Chi-square.

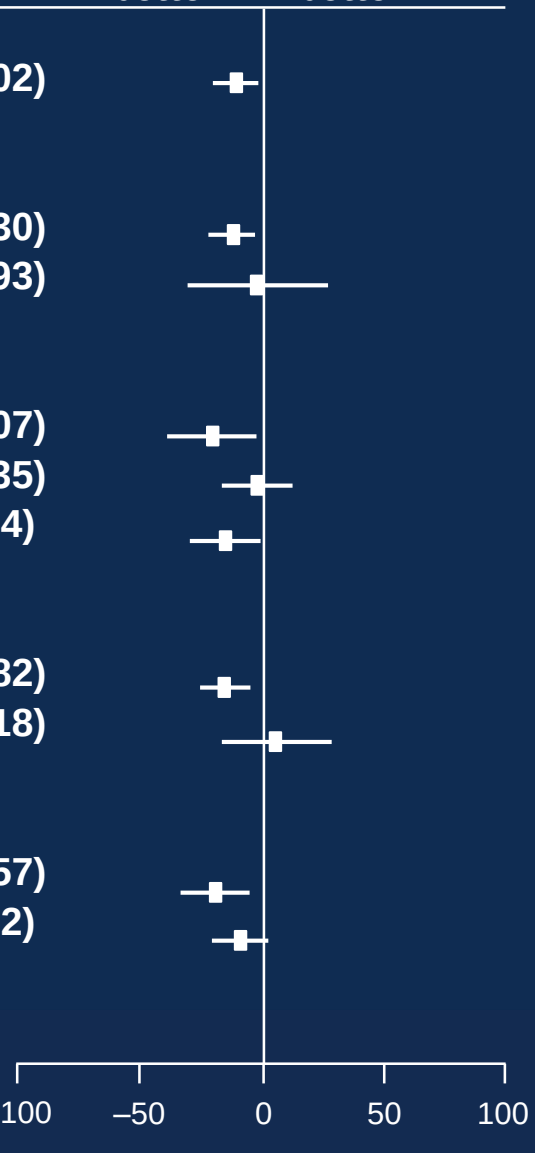
# pCR by Central ER/PR Receptor Status



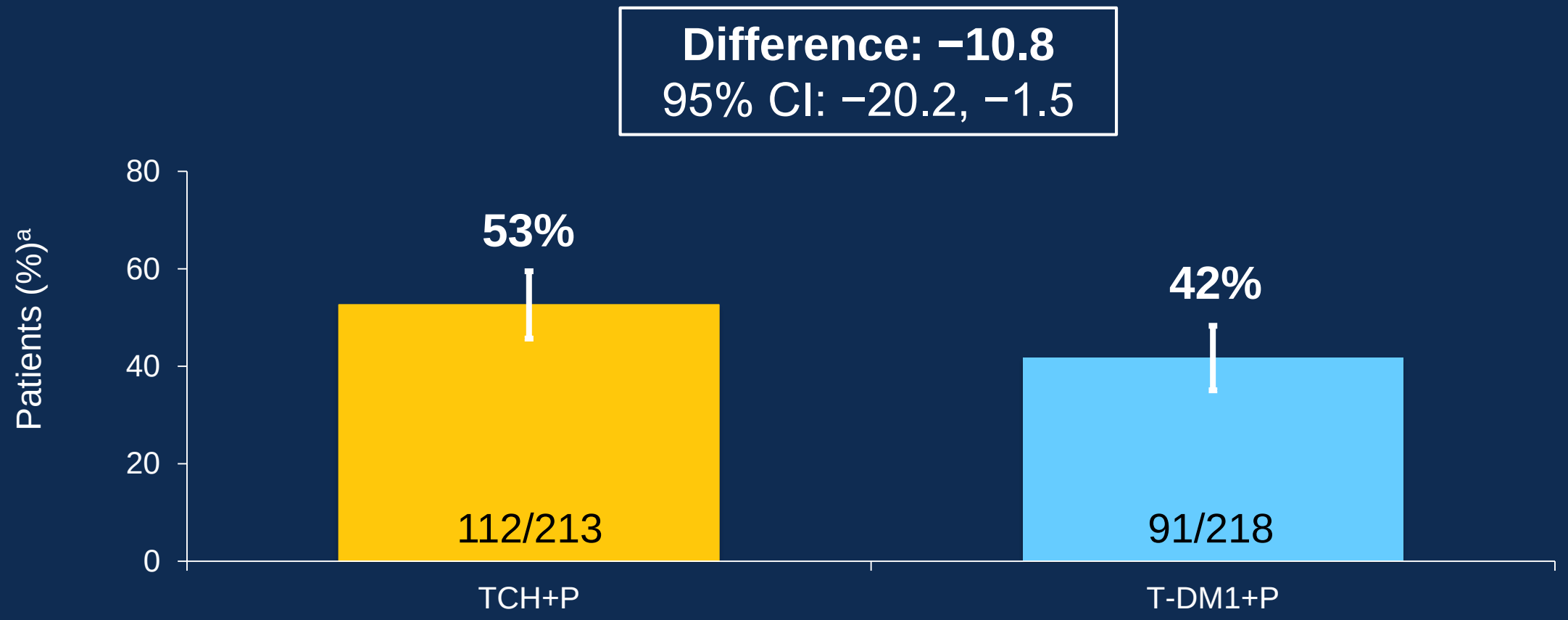

[a]ypT0/is, ypN0; patients with missing or unevaluable pCR status were considered nonresponders. Twenty patients had “unknown” ER/PR status by central analysis.

# pCR by Baseline Factors

| | TCH+P (n=221) | | T-DM1+P (n=223) | | Response Rate | |
|---|---|---|---|---|---|---|
| | n | Responder, % | n | Responder, % | Difference | 95% CI |
| All patients | 221 | 55.7 | 223 | 44.4 | –11.26 | (–20.50, –2.02) |
| Age group | | | | | | |
| <65 | 200 | 57.5 | 198 | 45.5 | –12.05 | (–21.79, –2.30) |
| ≥65 | 21 | 38.1 | 25 | 36.0 | – 2.10 | (–30.12, 25.93) |
| World region | | | | | | |
| North America | 54 | 53.7 | 54 | 33.3 | –20.37 | (–38.67, –2.07) |
| Rest of the world | 83 | 51.8 | 84 | 50.0 | –1.81 | (–16.97, 13.35) |
| Western Europe | 84 | 60.7 | 85 | 45.9 | –14.83 | (–29.71, 0.04) |
| Clinical stage at diagnosis | | | | | | |
| II–IIIA | 183 | 57.9 | 186 | 43.0 | –14.91 | (–25.00, –4.82) |
| IIIB–IIIC | 38 | 44.7 | 37 | 51.4 | 6.61 | (–15.95, 29.18) |
| Central ER/PR status | | | | | | |
| ER and PR negative | 82 | 73.2 | 83 | 54.2 | –18.95 | (–33.34, –4.57) |
| ER and/or PR positive | 128 | 43.8 | 131 | 35.1 | –8.64 | (–20.50, 3.22) |



# Breast Conserving Surgery Rates

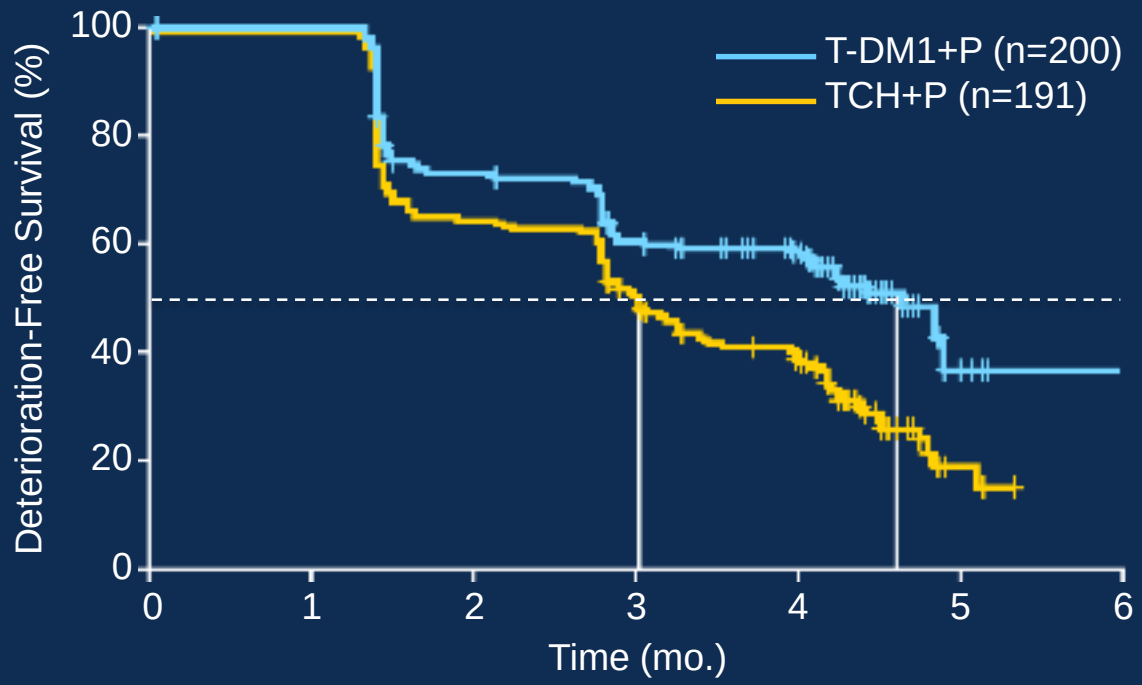



[a]ITT population of patients without inflammatory breast cancer patients.

# Maintenance of HRQoL and Physical Function

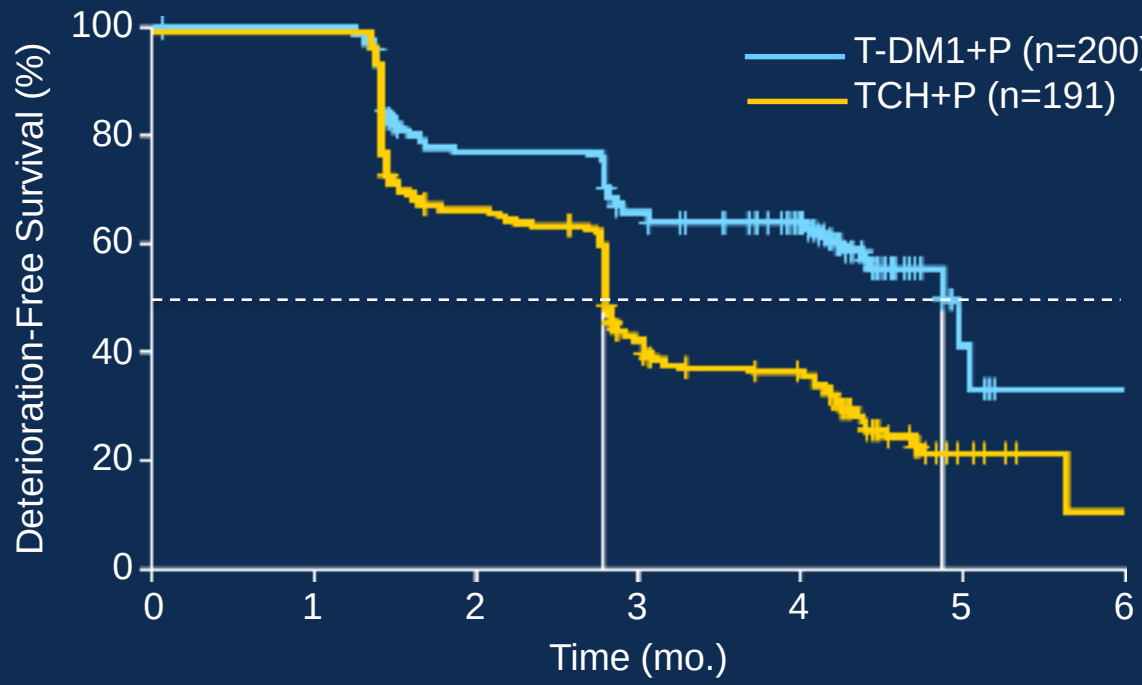
## Maintenance of HRQoL[a]

HR (95% CI): 0.60 (0.46–0.78)




## Maintenance of physical function[a]

HR (95% CI): 0.47 (0.36–0.62)




[a]Data are based on the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and QLQ-modified breast cancer module (BR23). Maintenance of health-related quality of life (HRQoL) and physical function were assessed as the time to deterioration defined as the time from baseline to first 10-point (or greater) decrease.

Only data from the neoadjuvant treatment phase including pre-surgery visit are used. Patients of the ITT population with a baseline assessment and at least 1 post-treatment assessment are included in this analysis.

# Treatment Exposure and Overview of Adverse Events: Neoadjuvant Phase

| | TCH+P (n=219)[a] | T-DM1+P (n=223)[a] |
|---|---|---|
| Median number of cycles (min–max) | 6 (1–6) | 6 (2–6) |
| Any adverse event, % | 98.6 | 88.3 |
| Serious adverse event, % | 28.8 | 4.9 |
| Grade ≥3 adverse event, % | 64.4 | 13.0 |
| Adverse event leading to treatment discontinuation of any component, % | 8.7 | 3.1 |
| LVEF <50% and ≥10% points decrease from baseline, % | 0.5 | 0.4 |

- Serious adverse events occurring in ≥1% of patients in the TCH+P arm: febrile neutropenia (12%), neutropenia (3%), diarrhea (4%), vomiting (1.8%), colitis (1%), and neutrophil count decreased (1%).
- No single serious adverse event occurred in ≥1% of patients in the T-DM1+P arm.

[a]Safety population.
LVEF, left ventricular ejection fraction.

# Grade ≥3 Adverse Events With Incidence of ≥3% in Either Treatment Arm: Neoadjuvant Phase

| Adverse event preferred term, % | TCH+P (n=219)[a] | T-DM1+P (n=223)[a] |
|---|---|---|
| Neutropenia | 25.1 | 0.4 |
| Diarrhea | 15.1 | 0.9 |
| Febrile neutropenia | 15.1 | 0 |
| Anemia | 9.6 | 0.9 |
| Neutrophil count decreased | 9.1 | 0 |
| Platelet count decreased | 5.0 | 1.3 |
| Fatigue | 3.2 | 1.3 |
| White blood cell count decreased | 4.1 | 0 |
| Hypertension | 3.2 | 0.4 |
| Vomiting | 3.2 | 0.4 |

[a]Safety population.

# Conclusions

- Neoadjuvant TCH+P achieved a superior pCR rate compared with T-DM1+P (56% vs 44%)
- Neoadjuvant TCH+P was associated with a higher BCS rate (53% vs 42%)
- Neoadjuvant T-DM1+P had a more favorable safety profile
  - Lower incidence of grade ≥3 adverse events (13% vs 64%), serious adverse events (5% vs 29%), and adverse events leading to treatment discontinuation (3% vs 9%)
- Neoadjuvant T-DM1+P was associated with longer maintenance of patient-reported HRQoL and physical function

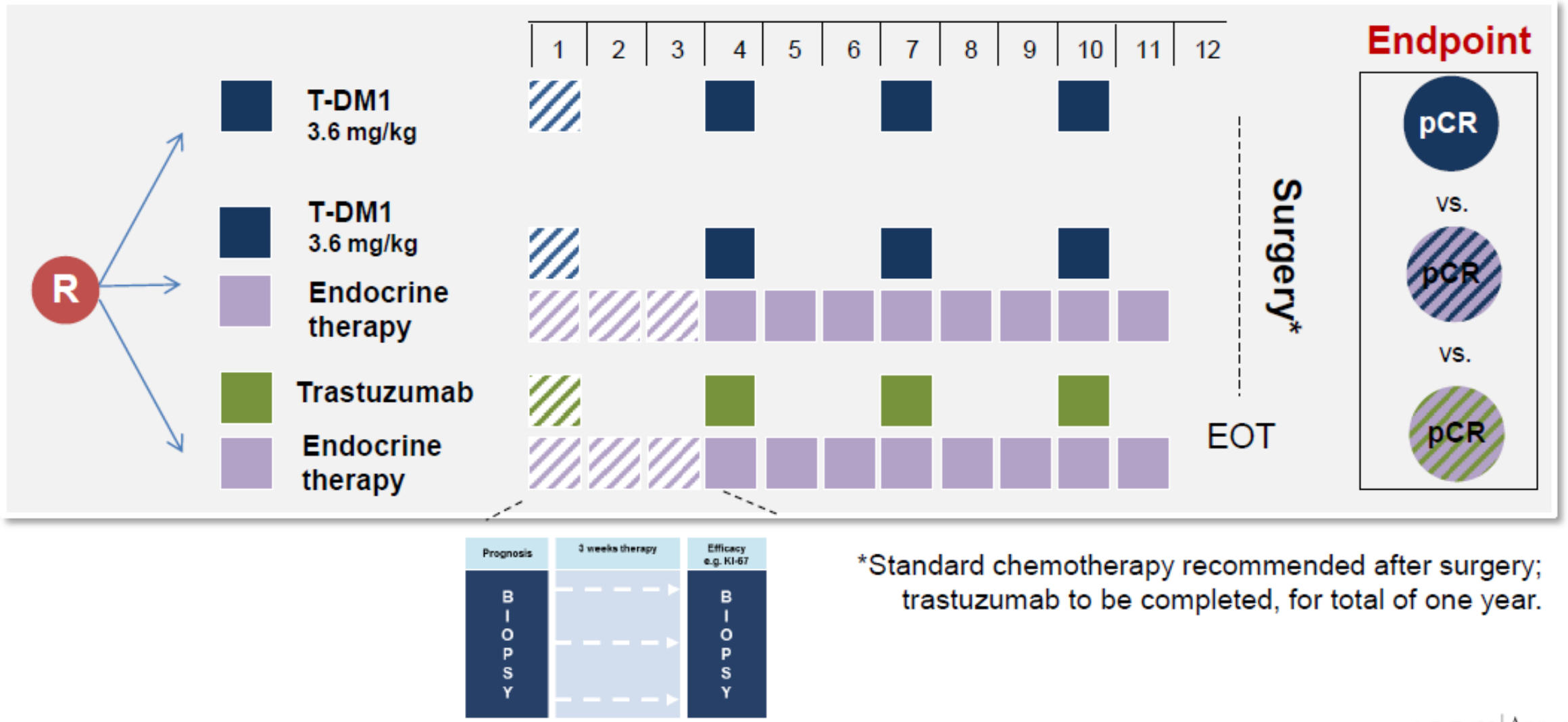
Upcoming phase III T-DM1 data in EBC: KATHERINE – T-DM1 vs trastuzumab adjuvant in patients without pCR; KAITLIN – T-DM1+P vs HP+taxane adjuvant.

# ADAPT HER2+/HR+: Rationale

- In HER2+ early breast cancer, current standard (chemo- + anti-HER2 therapy) is independent of hormone receptor (HR) status
- HER2+/HR+ (*triple positive*) breast cancer is a distinct entity
- pCR after neoadjuvant chemo- + anti-HER2 therapy:
  - rates differ according to HR-status
  - impact on survival differs according to HR-status
- Combined targeted blockade (endocrine + anti-HER2 therapy) without systemic chemotherapy may be an effective neoadjuvant strategy

Cortazar et al, Lancet 2014; Rimawi et al, JCO 2013

# ADAPT HER2+/HR+: Trial Design

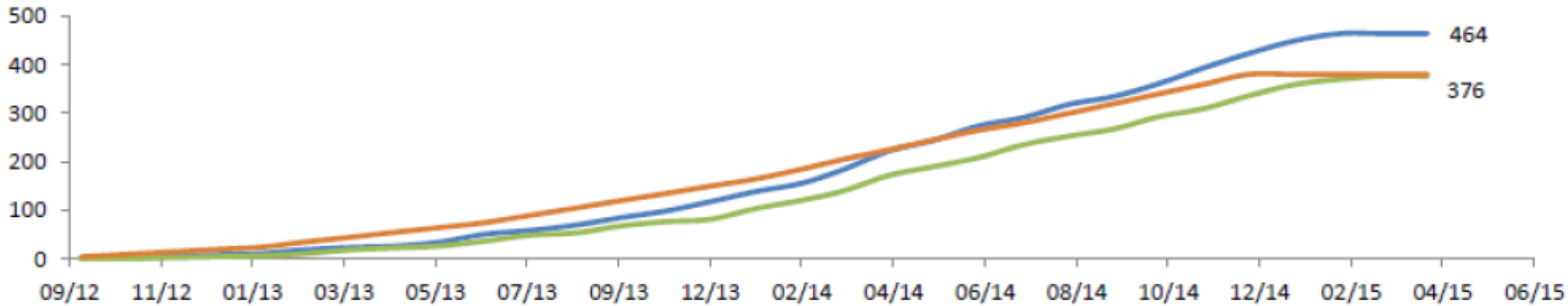



*Standard chemotherapy recommended after surgery; trastuzumab to be completed, for total of one year.

# ADAPT HER2+/HR+: Key Inclusion criteria

- Confirmed ER and/or PR positive (≥1%) and HER2+ by *central* pathology
- cT1c - cT4a-c
- All cN
- No clinical evidence for distant metastasis (M0)
- Adequate organ function
- LVEF ≥ 50%; LVEF within normal institutional limits by echocardiography; normal ECG

# ADAPT HER2+/HR+: Recruitment




- Screened patients
- Randomized patients
- Planned randomization

n = 48 active sites (51 total)

# ADAPT HER2+/HR+: Interim Analysis

WSG
WOMEN'S HEALTHCARE STUDY GROUP

- Primary trial endpoint: Comparison of pCR rates of each T-DM1 arm (± ET) vs. trastuzumab + endocrine therapy
  (assumption 25% vs. 10%; power 80%, alpha 2.5% each, one sided)
- pCR: no invasive carcinoma in breast and nodes
- Pre-planned interim analyses after first 130 patients:
  - evaluate pCR rates and their correlations with early response markers (changes between initial and 3-week biopsy)
  - assure safety of study medications
- Interim analyses presented to DSMB in January 2015

# ADAPT HER2+/HR+: Baseline patient and tumor characteristics

| | A (T-DM1) | B (T-DM1+ET) | C (Trast. + ET) |
|---|---|---|---|
| N | 37 | 48 | 45 |
| median age | 46 years | 51 years | 48 years |
| **premenopausal** | **22 (59.5%)** | **22 (45.8%)** | **27 (60.0%)** |
| postmenopausal | 15 (40.5%) | 26 (54.2%) | 18 (40.0%) |
| cT 1 | 15 (40.5%) | 22 (45.8%) | 15 (33.3%) |
| **cT 2** | **17 (45.9%)** | **24 (50.0%)** | **26 (57.8%)** |
| **cT >=3** | **5 (13.5%)** | **2 (4.2%)** | **4 (8.9%)** |
| cN 0 | 23 (62.2%) | 35 (72.9%) | 31 (68.9%) |
| **cN 1** | **11 (29.7%)** | **12 (25.0%)** | **12 (26.7%)** |
| **cN >=2** | **3 (8.1%)** | **1 (2.1%)** | **2 (4.4%)** |
| ER positive | 36 (97.3%) | 47 (97.9%) | 44 (97.8%) |
| ER negative | 1 (2.7%) | 1 (2.1%) | 1 (2.2%) |
| PR positive | 34 (91.9%) | 43 (89.6%) | 37 (82.2%) |
| PR negative | 3 (8.1%) | 5 (10.4%) | 8 (17.8%) |
| central G1/2 (mostly G2) | 8 (21.6%) | 10 (20.8%) | 14 (31.1%) |
| **central G3** | **29 (78.4%)** | **38 (79.2%)** | **31 (68.9%)** |
| **Ki67 (median)** | **35%** | **35%** | **30%** |

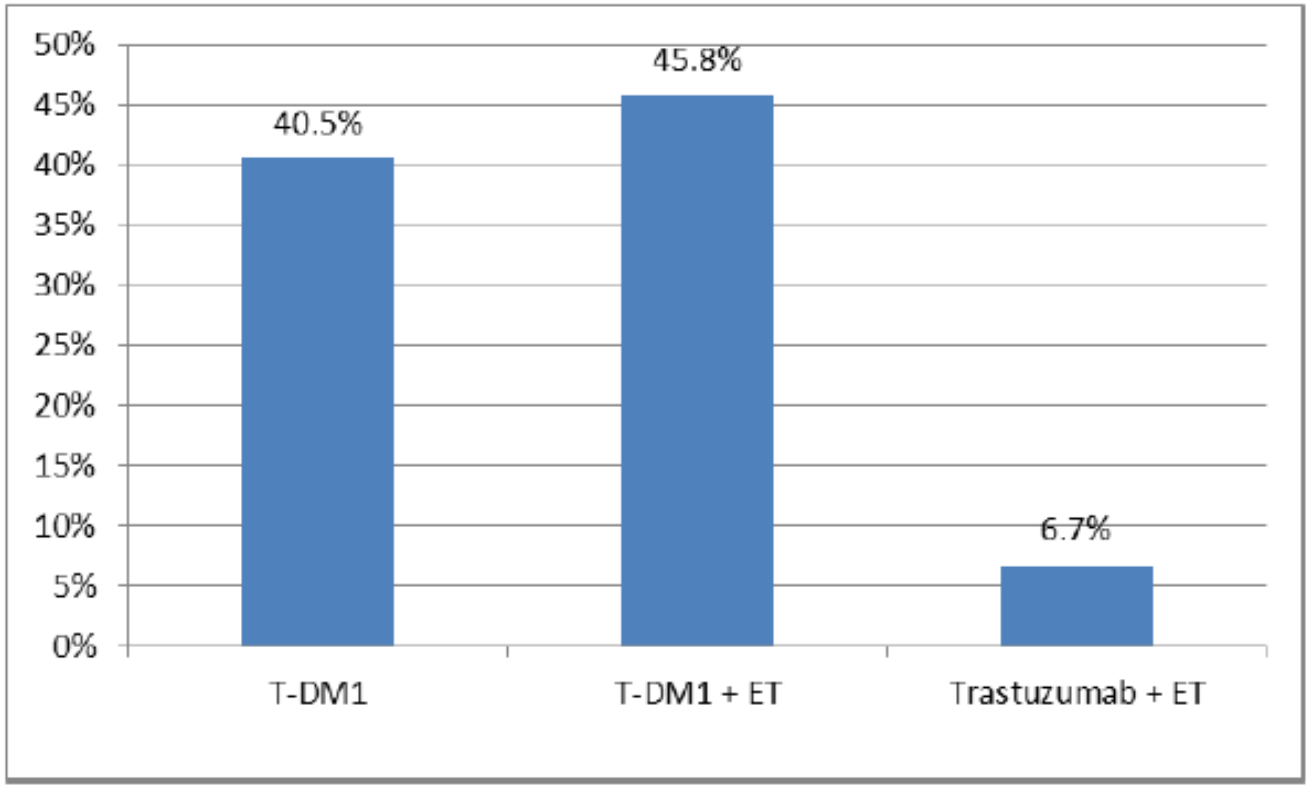
# ADAPT HER2+/HR+: Safety

- Study medication administered for 4 cycles:
  - 100% T-DM1; 95.8% T-DM1 + ET; 95.2% T+ET
- 16 serious adverse events in 13 patients (all CTCAE grades 1-3)
- 14 termed serious due to unplanned hospitalization, 7 related to study medication; all patients recovered completely

| Parameter | T-DM1 | | T-DM1 + ET | | Trastuzumab + ET | |
|---|---|---|---|---|---|---|
| **Liver Function Investigation** | **all CTC** | **CTC 3** | **all CTC** | **CTC 3** | **all CTC** | **CTC 3** |
| Blood bilirubin increased | 3% | 3% | 0% | 0% | 0% | 0% |
| Gamma glutamyltransferase increased | 5% | 0% | 2% | 0% | 0% | 0% |
| Aspartate aminotransferase increased | 19% | 5% | 10% | 0% | 0% | 0% |
| Alanine aminotransferase increased | 22% | 3% | 6% | 0% | 2% | 0% |
| Alkaline phosphatase increased | 0% | 0% | 0% | 0% | 4% | 0% |
| Hepatotoxicity | 3% | 0% | 4% | 2% | 0% | 0% |
| **Blood and lymphatic disorders** | | | | | | |
| Neutropenia | 0% | 0% | 2% | 0% | 0% | 0% |
| Thrombocytopenia | 30% | 3% | 15% | 0% | 4% | 0% |
| **Infections and infestations** | 11% | 0% | 15% | 2% | 9% | 0% |
| **n** | | 37 | | 48 | 45 | |

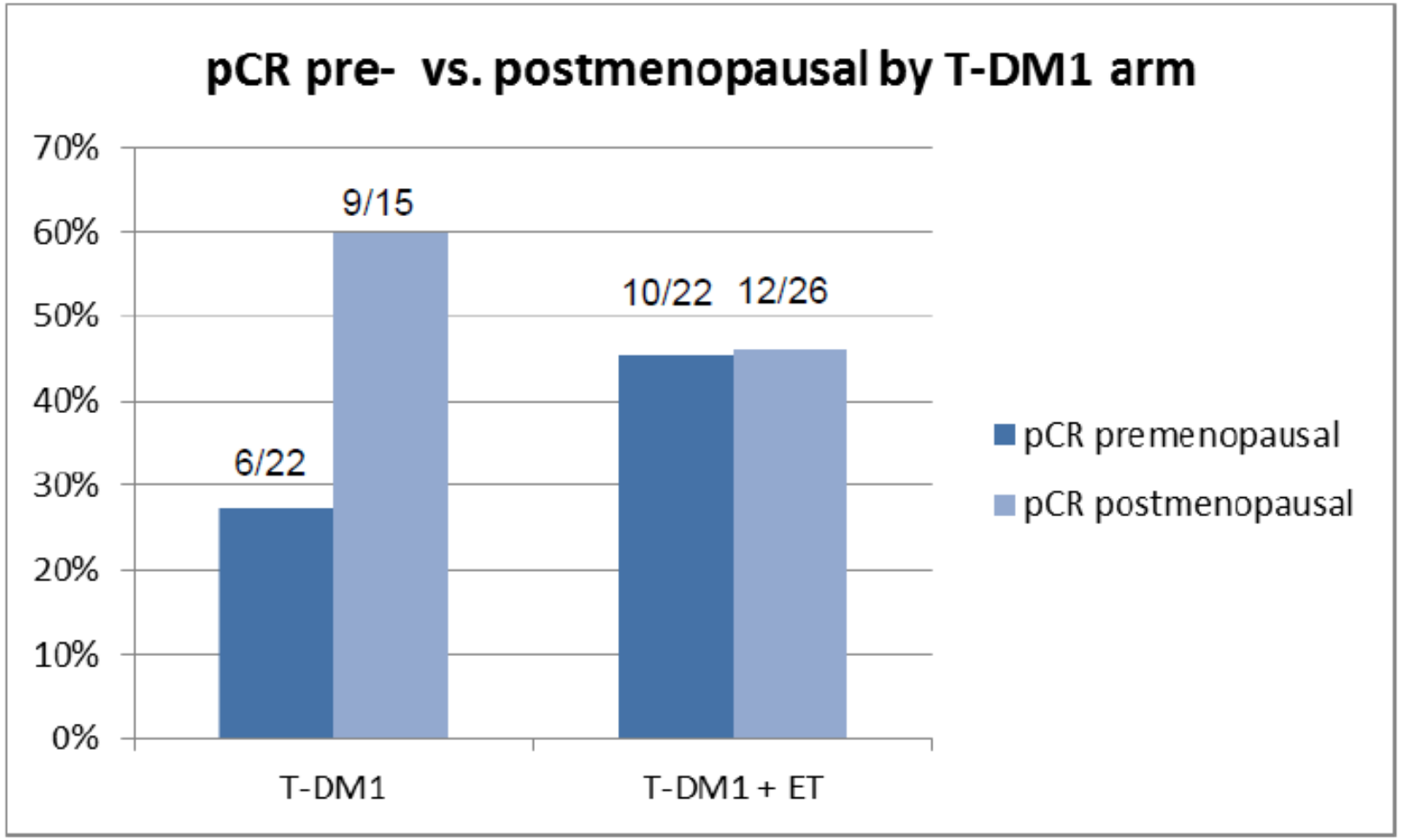
no reported CTCAE grade 4 events

# ADAPT HER2+/HR+: pCR
## (no invasive tumor in breast and nodes)




- pCR rates substantially higher in T-DM1 containing arms ($p<0.001$ A or B vs. C)

# ADAPT HER2+/HR+: Efficacy of adding endocrine therapy to T-DM1 differs by menopausal status (exploratory analysis)

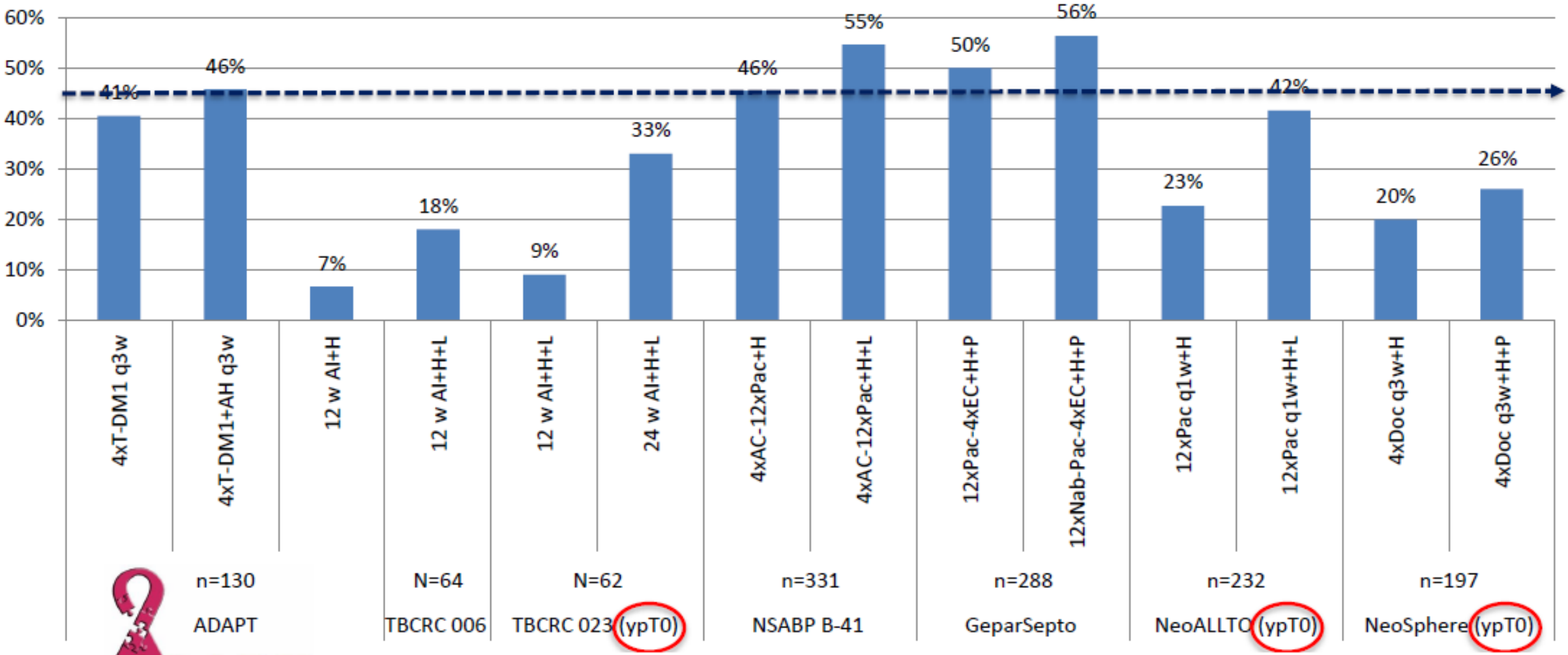





PRESENTED AT: ASCO Annual '15 Meeting

# pCR rates in HER+/HR+ early breast cancer

WSG
WOMEN'S HEALTHCARE STUDY GROUP



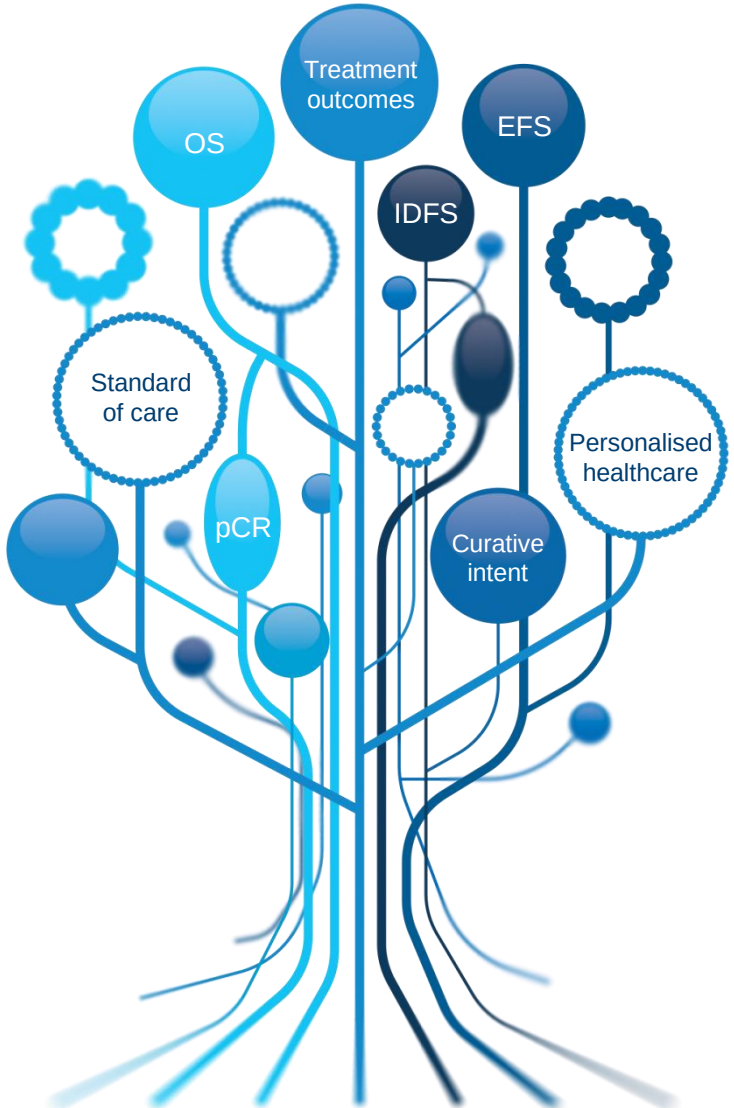

Rimawi et al, 2013; Rimawi et al, 2014; Robidoux et al, 2013; Untch et al, 2014; Baselga et al, 2012; Gianni et al, 2012.

# ADAPT HER2+/HR+: Conclusions from pre-planned interim analysis

- **More than 40% pCR (breast and nodes) in T-DM1 treated patients** after 12 weeks without *systemic* chemotherapy:
  - 40.5% T-DM1; 45.8% T-DM1 + ET; 6.7% trastuzumab + ET
- **Very low overall toxicity**; no new safety signals detected
- Adding endocrine therapy to T-DM1 increases pCR in pre- but not in postmenopausal patients (exploratory analysis)
- Early response biomarkers:
  - No trend for Ki-67 (3-week vs. baseline) as predictor of pCR
  - Early therapy effect impacted Ki-67 quantification in 3-week biopsy (low cellularity in 43.1%) and was associated with pCR

# HER2+ HR+ early breast cancer: Future perspectives

- Therapy de-escalation is possible
- TDM-1 single agent warrants further evaluation
- Full data set needed to substantiate interim findings:
  - Confirm efficacy and impact of additional endocrine therapy
  - Assess early-response biomarkers, mutation analysis, and subtypes
- Comparison T-DM1 single agent vs. standard chemotherapy + dual blockade (trastuzumab + pertuzumab) needed




# Need for treatment escalation with incorporation of newer modalities

## *Adding endocrine therapy in neoadjuvant setting for triple positive tumours?*

# NSABP B-52 (NRG Oncology)

## Evaluating Pathologic Complete Response Rates in Patients with Hormone Receptor-Positive, HER2-Positive Breast Cancer treated with Neoadjuvant Therapy of Docetaxel, Carboplatin, Trastuzumab, and Pertuzumab (TCHP) with or without Concurrent Estrogen Deprivation Therapy

Mothaffar F. Rimawi, Reena S. Cecchini, Priya Rastogi, Charles E. Geyer, Jr, Louis Fehrenbacher, Philip J. Stella, Zoneddy Dayao, Rachel Rabinovitch, Stephen H. Dyar, Patrick J. Flynn, Luis Baez-Diaz, Soonmyung Paik, Sandra M. Swain, Eleftherios P. Mamounas, C. Kent Osborne, Norman Wolmark

NRG ONCOLOGY

Advancing Research. Improving Lives.™

# Dual HER2 inhibition by ER status

| Trial | HER2 Inhibition | pCR in ER-positive | pCR in ER-negative |
|---|---|---|---|
| **NeoSphere** | Per/Tras | 26% | 63% |
| **NeoALTTO** | Lap/Tras | 42% | 61% |
| **CALGB 40601** | Lap/Tras | 42% | 77% |
| **NSABP B-41** | Lap/Tras | 56% | 73% |
| **TRYPHAENA** | Per/Tras | 46-50% | 65-84% |

# Rationale

- ER+/HER2+ tumors are less likely than ER-/HER2+ tumors to respond to dual anti-HER2 therapy.
- ER may act as a pathway of resistance to anti-HER2 treatment.
- Older trials suggested antagonistic effects of chemotherapy and endocrine therapy.

# Hypothesis

- **We hypothesized that concurrent inhibition of ER and HER2, plus chemotherapy, will not be antagonistic, and will overcome resistance to treatment thus improving pCR rates in pts with ER+/HER2+ breast cancer.**

# NRG Oncology/NSABP B-52

**HER2-Positive, ER and/or PgR-Positive Invasive Breast Cancer Diagnosed by Core Needle Biopsy**

**REQUIRED BLOOD AND TISSUE**

**STRATIFICATION**

**RANDOMIZATION**

**Arm 1**

**TCH**
**every 21 days x 6 cycles**
**+**
**Pertuzumab**
**every 21 days x 6 cycles**

**REQUIRED TISSUE**
Core biopsy of primary tumor
***before Cycle 3*** of TCHP*

***Obtained core biopsy in 103 pts.**

**Arm 2**

**TCH**
**every 21 days x 6 cycles**
**+**
**Pertuzumab**
**every 21 days x 6 cycles**
**+**
**Estrogen Deprivation**

**SURGERY (lumpectomy or mastectomy) and axillary staging**

# Eligibility Criteria

- **Invasive adenocarcinoma of the breast *diagnosed by core needle biopsy***
- **Clinical tumor ≥2.0 cm if clinically node negative. Any size if node positive.**
- **Tumors must be hormone receptor positive and HER2+ by ASCO/CAP**
- **The LVEF must be ≥50% regardless of the testing facility's lower limit of normal.**
- **Adequate organ function**

# Dose Regimen

- **TCH: Docetaxel 75 mg/m2 IV + carboplatin AUC of 6 IV + trastuzumab IV (administer a loading dose of 8mg/kg; then 6 mg/kg every 3 wks for the remaining doses).**
- **Pertuzumab: Administer a loading dose of 840 mg; then 420 mg every 3 wks for the remaining doses.**
- **Estrogen deprivation therapy determined by menopausal status:**

  *Postmenopausal:* **Aromatase inhibitor**

  *Premenopausal:* **Aromatase inhibitor plus ovarian suppression**

# Endpoints

## Primary

- pCR rate in the breast and nodes ($ypT_{0-is}$ $ypN_0$)

## Secondary

- pCR rate in the breast
- Clinical complete response
- Toxicity
- Recurrence-free interval
- OS

} ~ 8 yrs after start of trial

# NSABP B-52
## Patient Characteristics*

- **Age**
  - ≤ 49 — 46%
  - 50 – 59 — 32%
  - ≥ 60 — 22%
- **Race**
  - White — 79%
  - Black — 12%
  - Other/Unk — 9%

- **Tumor staging**
  - cT0-cT2 — 74%
  - cT3-cT4c — 24%
  - cT4d — 2%
- **Clinical Nodal Status**
  - Pos. — 57%
  - Neg. — 43%

*** Patient characteristics were balanced between treatment regimens**

# NSABP B-52
## Toxicity

| Toxicity | TCHP (n=154) | | | | TCHP +Est Dep (n=157) | | | |
|---|---|---|---|---|---|---|---|---|
| | Gr 0-1 | Gr 2 | Gr 3 | Gr 4 | Gr 0-1 | Gr 2 | Gr 3 | Gr 4 |
| Diarrhea | 42% | 34% | 23% | <1% | 43% | 35% | 22% | 0% |
| Nausea | 60% | 31% | 9% | 0% | 65% | 29% | 6% | 0% |
| Vomiting | 82% | 10% | 8% | <1% | 82% | 13% | 5% | 0% |
| Dehydration | 71% | 20% | 8% | <1% | 78% | 17% | 5% | 0% |

# NSABP B-52
## Toxicity

| Toxicity | TCHP (n=154) | | | | TCHP +Est Dep (n=157) | | | |
|---|---|---|---|---|---|---|---|---|
| | Gr 0-1 | Gr 2 | Gr 3 | Gr 4 | Gr 0-1 | Gr 2 | Gr 3 | Gr 4 |
| **Anemia** | 53% | 35% | 12% | 0% | 56% | 26% | 18% | 0% |
| **Hypokalemia** | 83% | 5% | 10% | 2% | 80% | 8% | 10% | 1% |
| **Febrile Neutropenia** | - | - | 5% | <1% | - | - | 7% | 1% |
| **Overall** | 3% | 29% | 59% | 10% | 5% | 37% | 52% | 6% |

# NSABP B-52
## Completion of Neoadjuvant Therapy

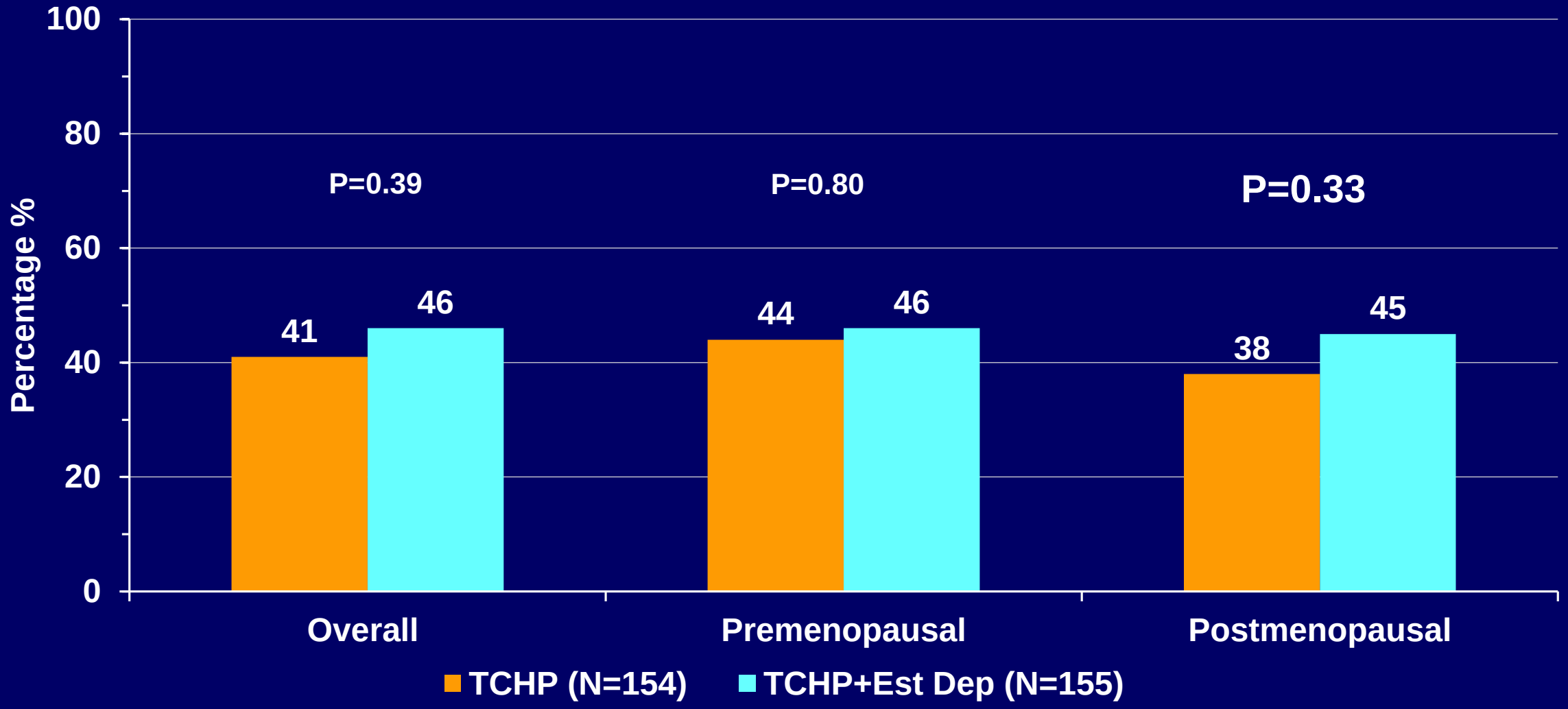
| | TCHP (n=158) | TCHP + Est Dep (n=157) |
|---|---|---|
| **TCHP*** | 89.9% | 90.4% |

*** Completed at least 5 cycles of all 4 drugs comprising TCHP**

# NSABP B-52
## Completion of Estrogen Deprivation among the TCHP+Est Dep Group

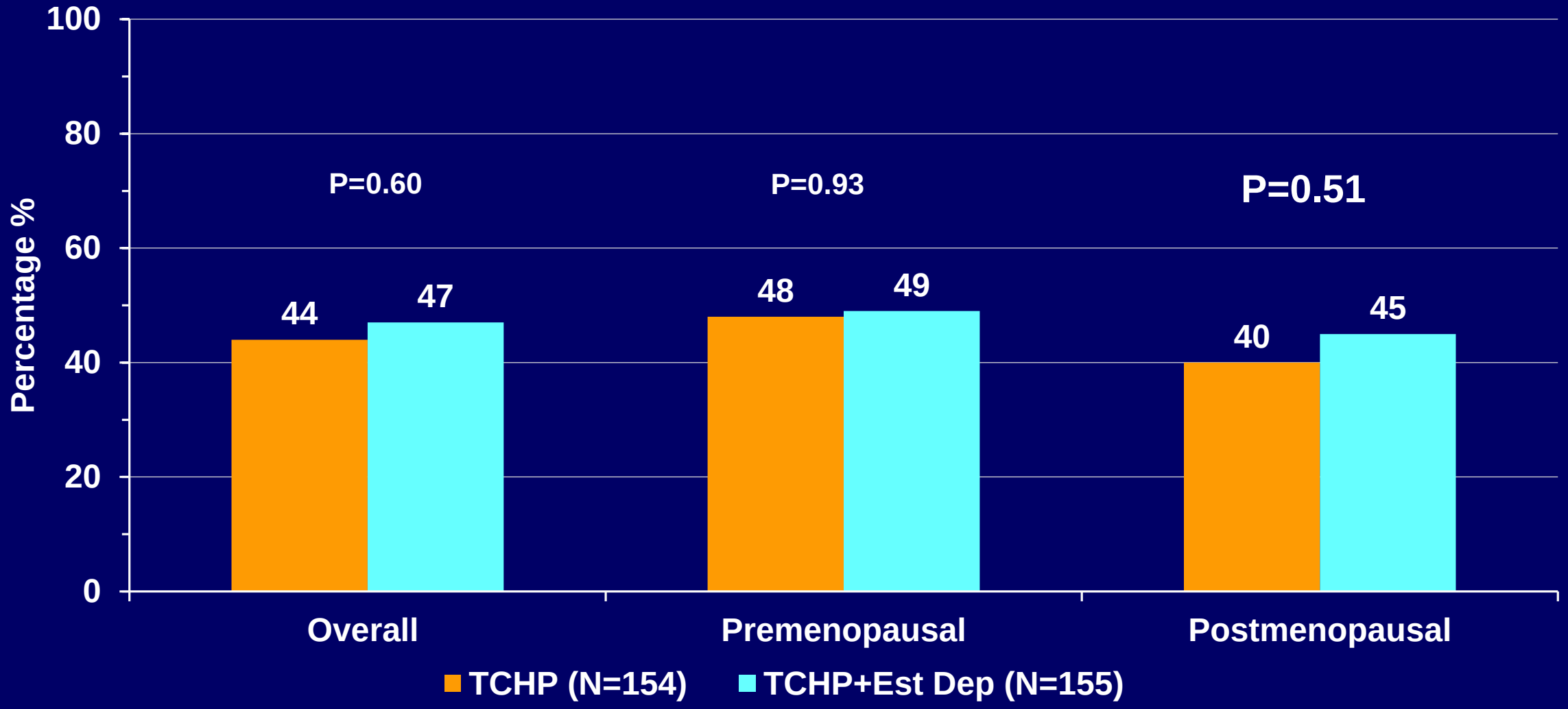
| | |
|---|---|
| **Aromatase Inhibitor** | |
| **% completed of total exp daily doses** | |
| ≥ 90% | 79.6% |
| 80–89% | 10.2% |
| < 80% | 10.2% |
| **Goserelin/LHRH agonist** (Among premenopausal women only) | 89.9% |

# NSABP B-52
## pCR Breast and Nodes



# NSABP B-52

## pCR Breast



# NSABP B-52
## Clinical Complete Response

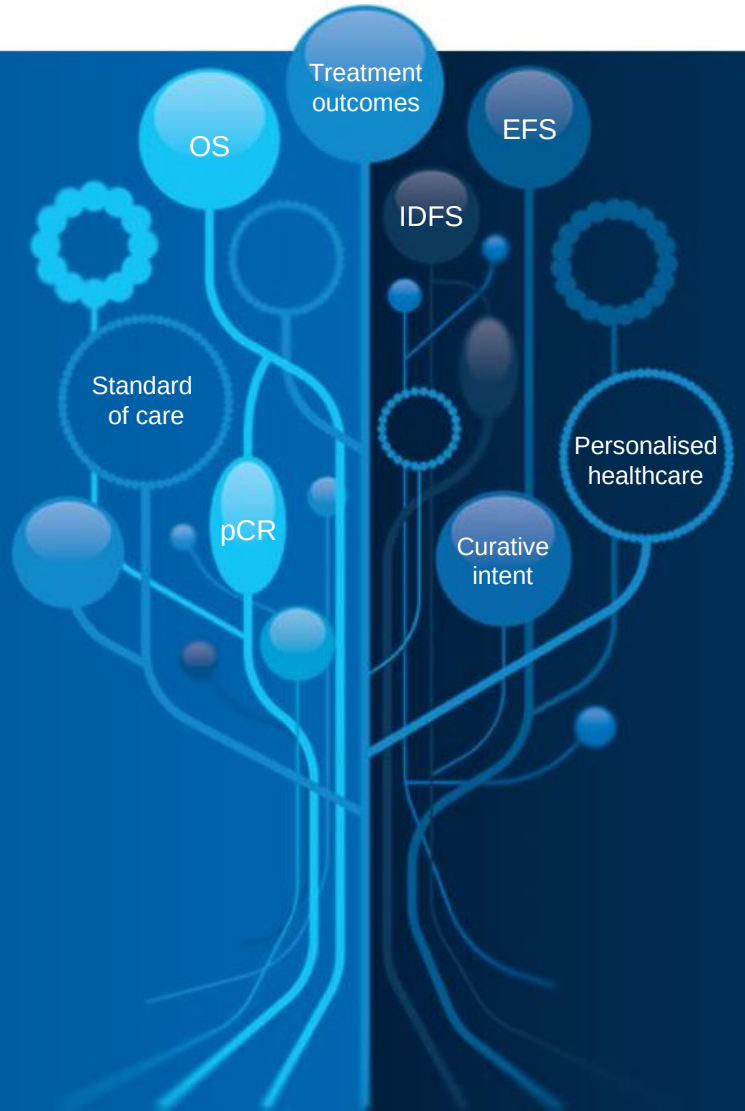
| cCR | TCHP (n=138) | TCHP + Est Dep (n=142) | p |
|---|---|---|---|
| Overall | 68.1% | 73.9% | 0.28 |

# NSABP B-52
## Surgery

| Type of Surgery | TCHP (n=158) | TCHP +Est Dep (n=157) |
|---|---|---|
| Lumpectomy | 33.5% | 42.7% |
| Mastectomy | 63.9% | 56.1% |
| No Surgery | 2.5% | 1.3% |

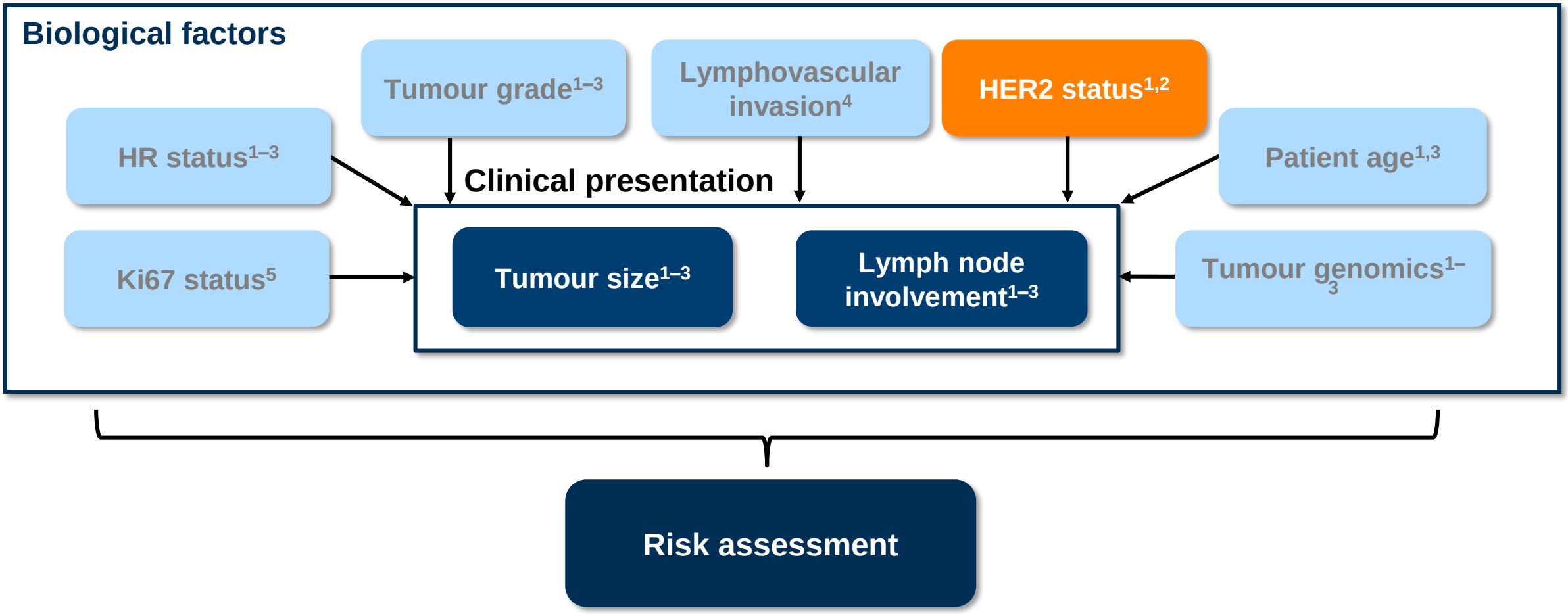
# Conclusion

- **The addition of estrogen deprivation to neoadjuvant chemotherapy was not antagonistic and did not increase toxicity.**
- **The combination increased pCR rates numerically, but the improvement was not statistically significant.**
- **Correlative science studies, evaluation of residual cancer burden (RCB), and long-term outcomes may help define the role of estrogen deprivation in the treatment of HER2+ early breast cancer.**



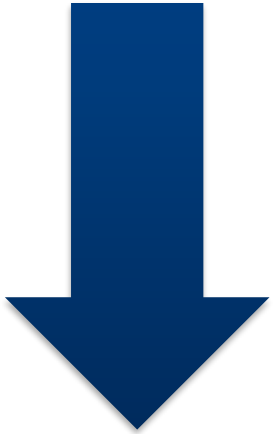

# Bridging neoadjuvant to adjuvant treatment

# Tumour biology and prognosis in trastuzumab-treated HER2-positive eBC patients is determined by a number of different risk factors



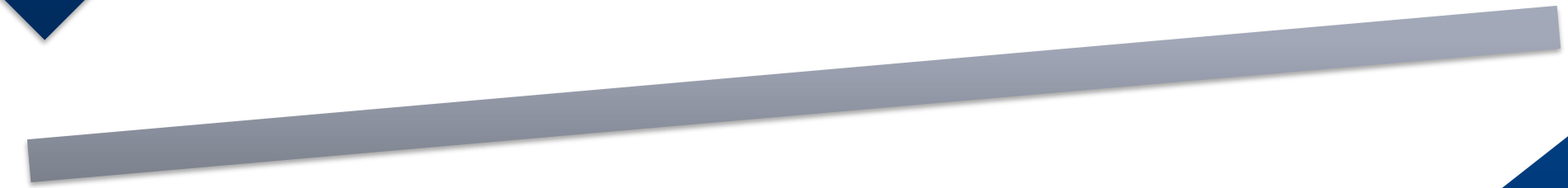

1. Martei YM & Matro JM. *Breast Cancer (Dove Med Press)* 2015; **7**:337–343;
2. Sparano JA, *et al*. *N Engl J Med* 2015; **373**:2005–2014; 3. Drukker CA, *et al*. *Int J Cancer* 2013; **133**:929–936;
4. Zhang S, *et al. BMC Cancer* 2017; **17**:335; 5. Inwald EC, *et al. Breast Cancer Res Treat* 2013; **139**:539–552.

# Evolving Standard of HER2 Treatment More or Less



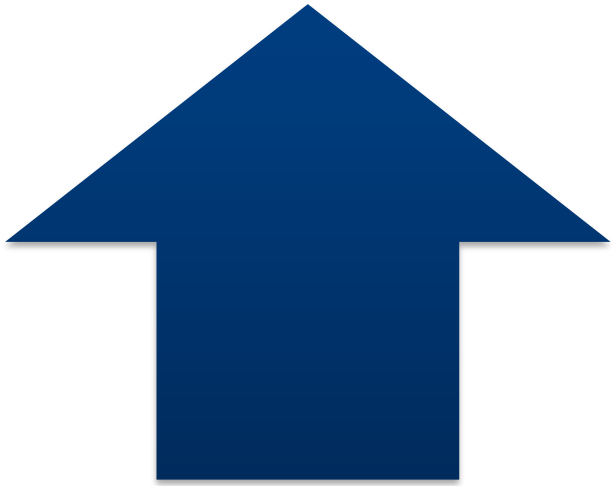
**De-escalation of Treatment**

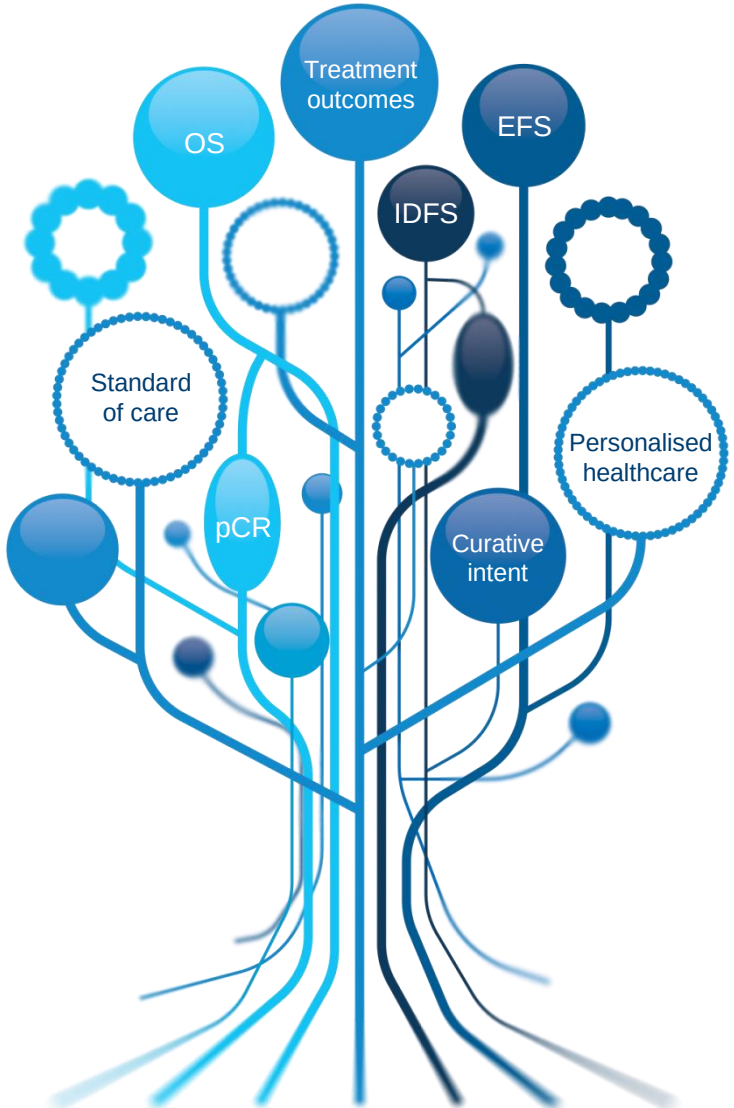
- T1a/T1b/T1c
- Certain Node Negative
- ? Immunomodulatory host factors



**Escalation (incorporation of newer tx)**

- Node positive
- LABC/Inflammatory
- ? no pCR
- ? Resistant Phenotype/Signatures



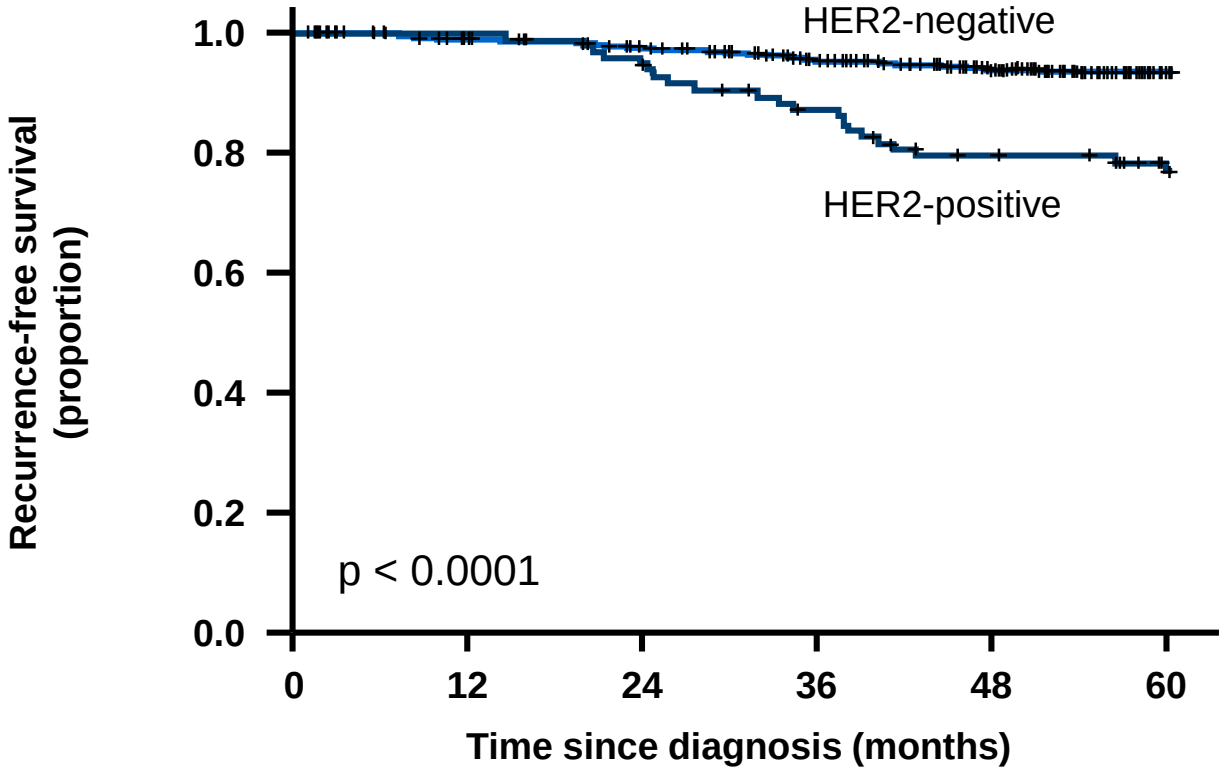



# Potential to de-escalate treatment for lower risk patients

*Node negative disease with small tumour size*

# The effect of HER2 status on survival of patients with small breast tumours

**No patient with HER2-positive breast cancer is 'low-risk'**




Analysis of 965 patients with T1a/b node-negative tumours who did not receive adjuvant systemic therapy revealed lower recurrence-free survival rates in patients with HER2-positive breast cancer than those with HER2-negative disease

•Gonzalez-Angulo AM, *et al. J Clin Oncol* 2009.

# Retrospective analysis of prognosis and relapse in patients with small HER2-positive tumours

| Group | No. of patients | No. of HER2-positive patients | Tumour grade | Key results and conclusions |
|---|---|---|---|---|
| Macarthur H, *et al.* | 99 | 99 | T1a,bN0 | • Significant results are obtained from overall study population (smaller than 2cm, node negative, HER2+ breast cancer)<br>• The 3-year loco-regional invasive recurrence-free, distant recurrence-free, invasive disease-free, and overall survival were 92% versus 98% (p= .0137), 95% versus 100% (p=.0072), 82% versus 97% (P < .0001), and 97% versus 99% (P = .18) for the ‘‘no trastuzumab’’ and ‘‘trastuzumab’’ cohorts, respectively. |
| Rodrigues MJ, *et al.* | 97 | 97 | T1a,bN0 | • Adjuvant trastuzumab improved 55-month recurrence free survival in patients with small tumours from 85% to 100% (p = 0.11, *non-significant) |
| Kelly CM, *et al.* | (386) | (386) | T1a,bN0M0 | • An analysis of the prognostic value of HER2 in patients with node-negative T1a/T1b concluded that HER2-positive cancers remains in the transition area between evidence and subjective judgement-based medicine |

**Evidence suggests trastuzumab treatment will increase survival of patients with small node-negative, HER2-postive tumours**

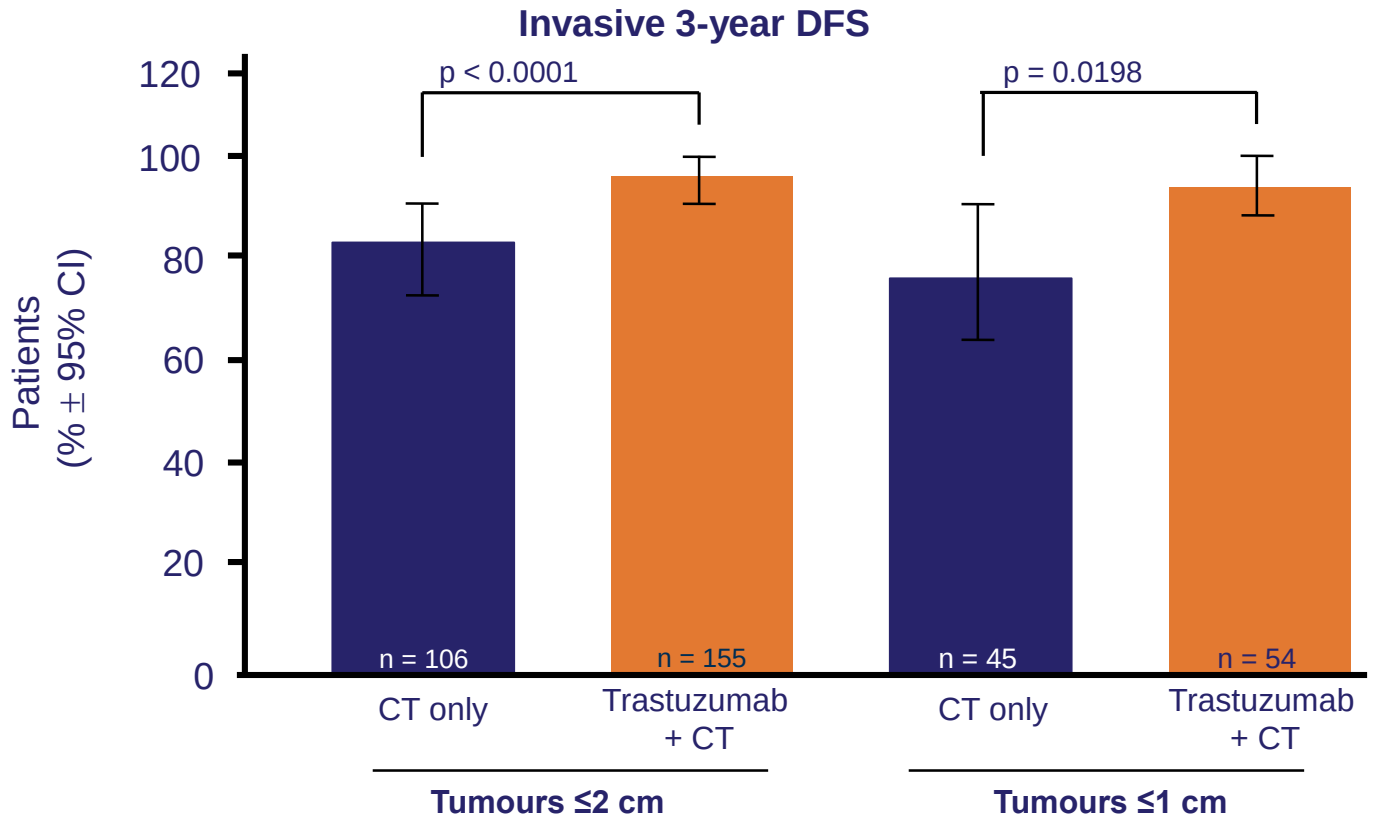
**Avoiding trastuzumab therapy will result in an otherwise avoidable recurrence**

•NS, non-significant

Macarthur H, *et al*. *Cancer* 2011;
•Rodrigues MJ, *et al*. *J Clin Oncol* 2010;
•Kelly CM, *et al*. *Ann Oncol* 2011.

# Trastuzumab plus chemotherapy is likely to benefit patients with small, node-negative, HER2-positive BC

**Trastuzumab plus chemotherapy improves DFS rates in small tumours compared with chemotherapy alone**




•BC, breast cancer; CT, chemotherapy; DFS, disease-free survival
•Macarthur H, *et al. Cancer* 2011.

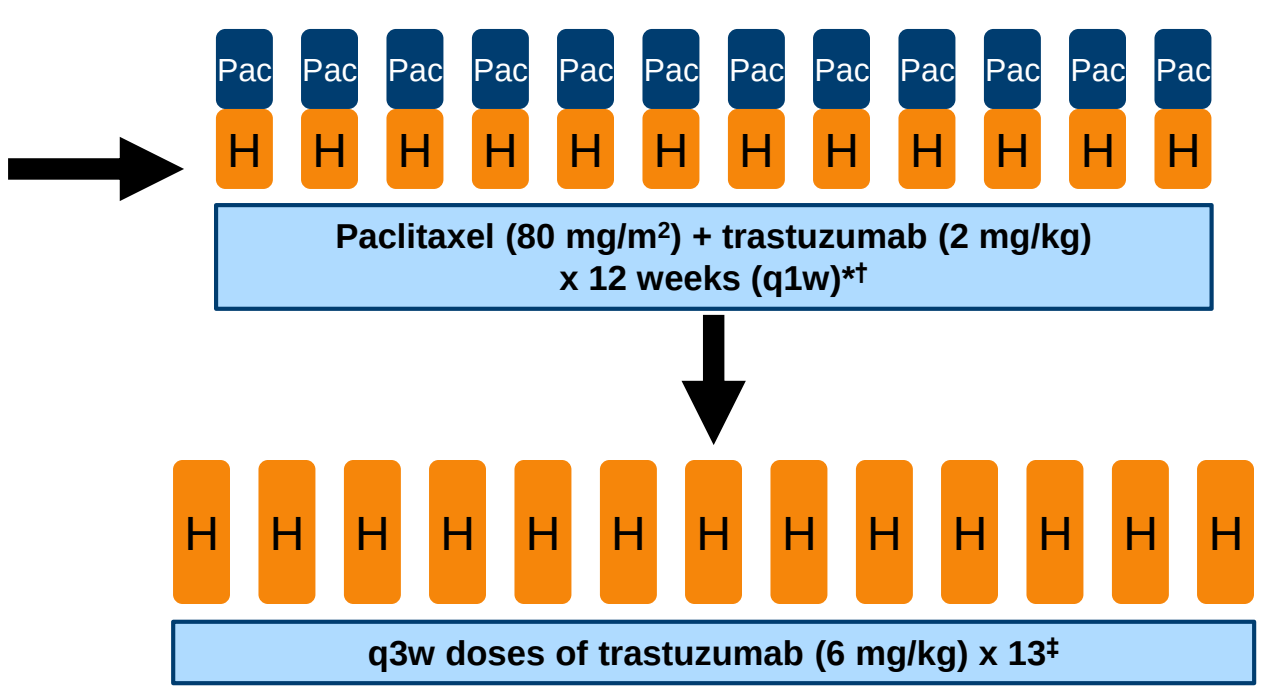
# APT (Tolaney) trial: Adjuvant paclitaxel and trastuzumab for HER2-positive breast cancer at lower risk of recurrence

- HER2-positive
- ER-positive or ER-negative
- Node-negative tumour ≤3 cm

**N = 406**

**Primary endpoint**

**IDFS**



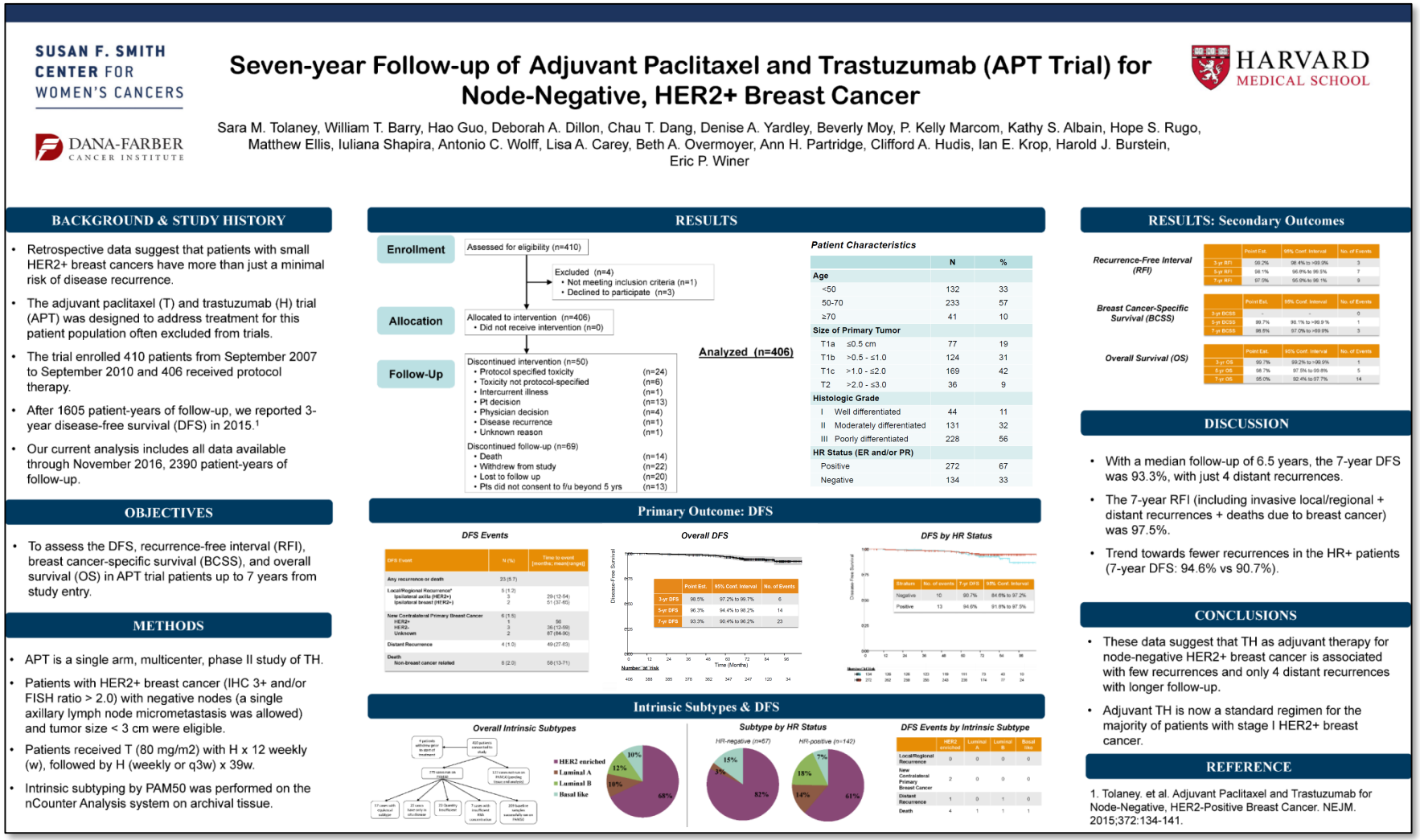

**Total 18 cycles of trastuzumab**

NOTE: This is a single-arm, single-centre study, so is unable to provide definitive data on treatment benefit

q1w, weekly; q3w, every 3 weeks.
* Loading dose of 4 mg/kg intravenous trastuzumab on Day 1.
† Radiation and hormonal therapy were initiated after completion of paclitaxel.
‡ Dosing could alternatively be 2 mg/kg intravenous q1w for 40 weeks.

Tolaney SM, *et al*. *N Engl J Med* 2015; **372**:134–141.

# APT (Tolaney) trial: Trastuzumab plus paclitaxel is effective in the treatment of patients at low risk of recurrence



SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

## Seven-year Follow-up of Adjuvant Paclitaxel and Trastuzumab (APT Trial) for Node-Negative, HER2+ Breast Cancer

Sara M. Tolaney, William T. Barry, Hao Guo, Deborah A. Dillon, Chau T. Dang, Denise A. Yardley, Beverly Moy, P. Kelly Marcom, Kathy S. Albain, Hope S. Rugo, Matthew Ellis, Iuliana Shapira, Antonio C. Wolff, Lisa A. Carey, Beth A. Overmoyer, Ann H. Partridge, Clifford A. Hudis, Ian E. Krop, Harold J. Burstein, Eric P. Winer

### BACKGROUND & STUDY HISTORY

- Retrospective data suggest that patients with small HER2+ breast cancers have more than just a minimal risk of disease recurrence.
- The adjuvant paclitaxel (T) and trastuzumab (H) trial (APT) was designed to address treatment for this patient population often excluded from trials.
- The trial enrolled 410 patients from September 2007 to September 2010 and 406 received protocol therapy.
- After 1605 patient-years of follow-up, we reported 3-year disease-free survival (DFS) in 2015.[1]
- Our current analysis includes all data available through November 2016, 2390 patient-years of follow-up.

### OBJECTIVES

- To assess the DFS, recurrence-free interval (RFI), breast cancer-specific survival (BCSS), and overall survival (OS) in APT trial patients up to 7 years from study entry.

### METHODS

- APT is a single arm, multicenter, phase II study of TH.
- Patients with HER2+ breast cancer (IHC 3+ and/or FISH ratio > 2.0) with negative nodes (a single axillary lymph node micrometastasis was allowed) and tumor size < 3 cm were eligible.
- Patients received T (80 mg/m2) with H x 12 weekly (w), followed by H (weekly or q3w) x 39w.
- Intrinsic subtyping by PAM50 was performed on the nCounter Analysis system on archival tissue.

### RESULTS

**Enrollment:** Assessed for eligibility (n=410)

Excluded (n=4)
- Not meeting inclusion criteria (n=1)
- Declined to participate (n=3)

**Allocation:** Allocated to intervention (n=406)
- Did not receive intervention (n=0)

**Follow-Up:** Analyzed (n=406)

Discontinued intervention (n=50)

| | |
|---|---|
| Protocol specified toxicity | (n=24) |
| Toxicity not protocol-specified | (n=6) |
| Intercurrent illness | (n=1) |
| Pt decision | (n=13) |
| Physician decision | (n=4) |
| Disease recurrence | (n=1) |
| Unknown reason | (n=1) |

Discontinued follow-up (n=69)

| | |
|---|---|
| Death | (n=14) |
| Withdrew from study | (n=22) |
| Lost to follow up | (n=20) |
| Pts did not consent to f/u beyond 5 yrs | (n=13) |

*Patient Characteristics*

| | N | % |
|---|---|---|
| **Age** | | |
| <50 | 132 | 33 |
| 50-70 | 233 | 57 |
| ≥70 | 41 | 10 |
| **Size of Primary Tumor** | | |
| T1a ≤0.5 cm | 77 | 19 |
| T1b >0.5 - ≤1.0 | 124 | 31 |
| T1c >1.0 - ≤2.0 | 169 | 42 |
| T2 >2.0 - ≤3.0 | 36 | 9 |
| **Histologic Grade** | | |
| I Well differentiated | 44 | 11 |
| II Moderately differentiated | 131 | 32 |
| III Poorly differentiated | 228 | 56 |
| **HR Status (ER and/or PR)** | | |
| Positive | 272 | 67 |
| Negative | 134 | 33 |

### Primary Outcome: DFS

*DFS Events*

| DFS Event | N (%) | Time to event, (months, mean(range)) |
|---|---|---|
| Any recurrence or death | 23 (5.7) | |
| Local/Regional Recurrence* | 5 (1.2) | |
| Ipsilateral axilla (HER2+) | 3 | 29 (12-54) |
| Ipsilateral breast (HER2+) | 2 | 51 (37-65) |
| New Contralateral Primary Breast Cancer | 6 (1.5) | |
| HER2+ | 1 | 56 |
| HER2- | 3 | 36 (12-59) |
| Unknown | 2 | 67 (64-90) |
| Distant Recurrence | 4 (1.0) | 49 (27-63) |
| Death | | |
| Non-breast cancer related | 6 (2.0) | 58 (13-71) |

*Overall DFS*




| | Point Est. | 95% Conf. Interval | No. of Events |
|---|---|---|---|
| 3-yr DFS | 98.5% | 97.2% to 99.7% | 6 |
| 5-yr DFS | 96.3% | 94.4% to 98.2% | 14 |
| 7-yr DFS | 93.3% | 90.4% to 96.2% | 23 |

*DFS by HR Status*




| Stratum | No. of events | 7-yr DFS | 95% Conf. Interval |
|---|---|---|---|
| Negative | 10 | 90.7% | 84.6% to 97.2% |
| Positive | 13 | 94.6% | 91.8% to 97.5% |

### Intrinsic Subtypes & DFS

*Overall Intrinsic Subtypes*




*Subtype by HR Status*




*DFS Events by Intrinsic Subtype*

| | HER2 enriched | Luminal A | Luminal B | Basal like |
|---|---|---|---|---|
| Local/Regional Recurrence | 0 | 0 | 0 | 0 |
| New Contralateral Primary Breast Cancer | 2 | 0 | 0 | 0 |
| Distant Recurrence | 1 | 0 | 1 | 0 |
| Death | 4 | 1 | 1 | 1 |

### RESULTS: Secondary Outcomes

*Recurrence-Free Interval (RFI)*

| | Point Est. | 95% Conf. Interval | No. of Events |
|---|---|---|---|
| 3-yr RFI | 98.2% | 96.4% to >99.9% | 3 |
| 5-yr RFI | 96.1% | 94.0% to 98.3% | 7 |
| 7-yr RFI | 97.9% | 95.9% to 99.1% | 9 |

*Breast Cancer-Specific Survival (BCSS)*

| | Point Est. | 95% Conf. Interval | No. of Events |
|---|---|---|---|
| 3-yr BCSS | - | - | 0 |
| 5-yr BCSS | 99.7% | 99.1% to >99.9% | 1 |
| 7-yr BCSS | 99.8% | 97.0% to >99.9% | 3 |

*Overall Survival (OS)*

| | Point Est. | 95% Conf. Interval | No. of Events |
|---|---|---|---|
| 3-yr OS | 99.7% | 99.2% to >99.9% | 1 |
| 5-yr OS | 98.7% | 97.5% to 99.8% | 5 |
| 7-yr OS | 95.0% | 92.4% to 97.7% | 14 |

### DISCUSSION

- With a median follow-up of 6.5 years, the 7-year DFS was 93.3%, with just 4 distant recurrences.
- The 7-year RFI (including invasive local/regional + distant recurrences + deaths due to breast cancer) was 97.5%.
- Trend towards fewer recurrences in the HR+ patients (7-year DFS: 94.6% vs 90.7%).

### CONCLUSIONS

- These data suggest that TH as adjuvant therapy for node-negative HER2+ breast cancer is associated with few recurrences and only 4 distant recurrences with longer follow-up.
- Adjuvant TH is now a standard regimen for the majority of patients with stage I HER2+ breast cancer.

### REFERENCE

1. Tolaney. et al. Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer. NEJM. 2015;372:134-141.

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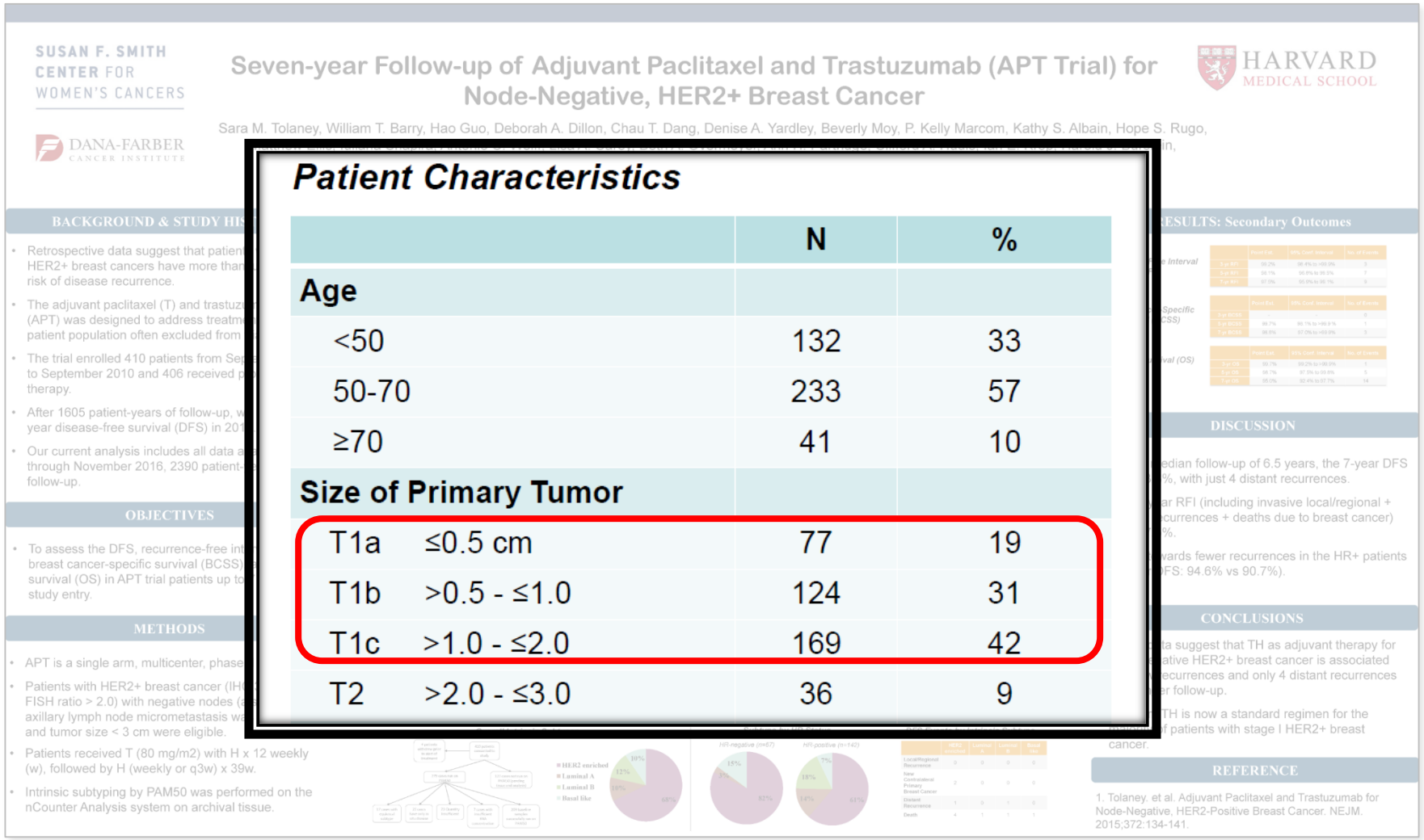

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HARVARD MEDICAL SCHOOL

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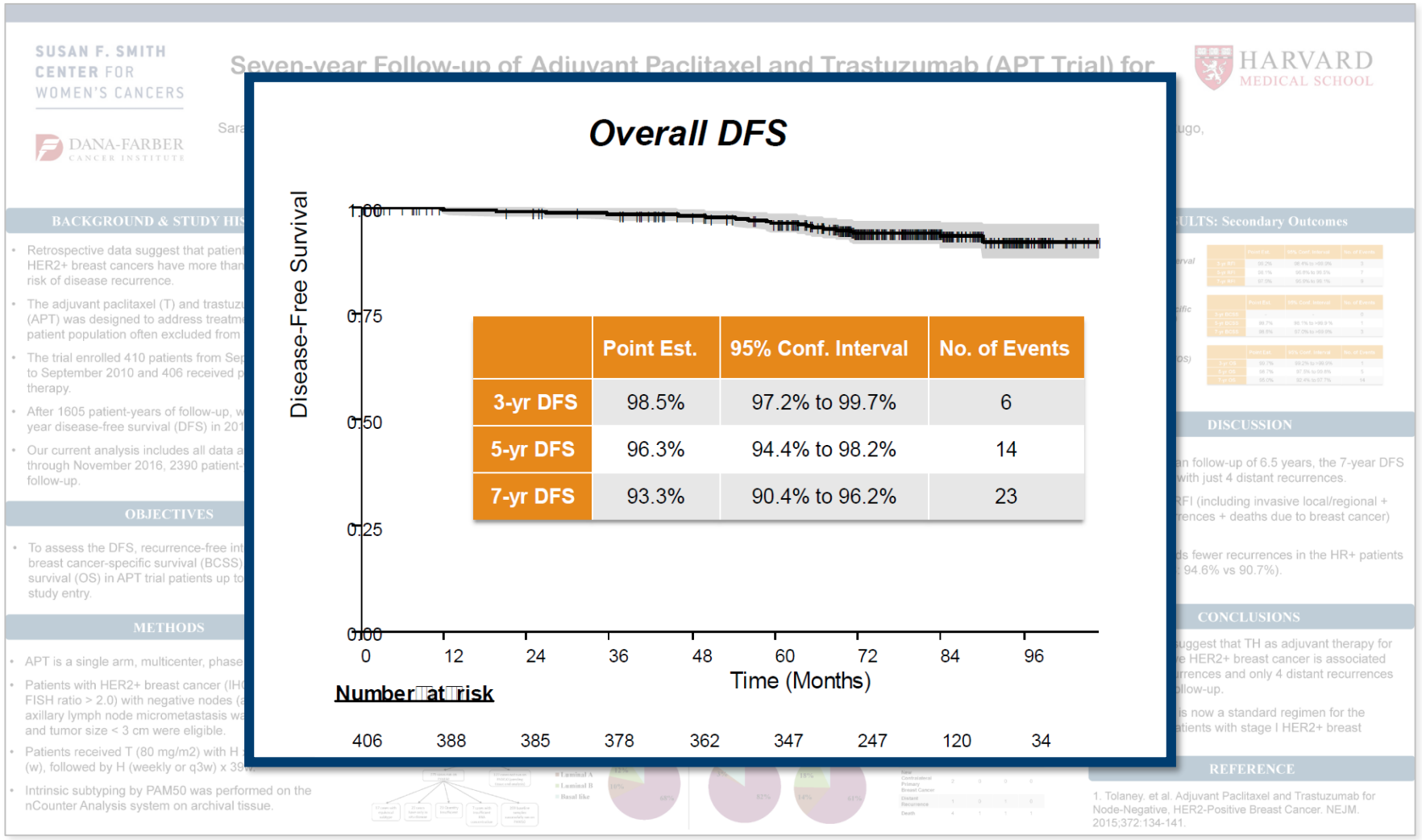


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Tolaney SM, *et al*. ASCO 2017 (Abstract 511; poster presentation).

# International guidelines recommend the APT treatment regimen for patients with small, node-negative tumours

**St. Gallen Expert Consensus**

**Primary Breast Cancer Clinical Practice Guidelines**

## Adjuvant therapy: HER2 targeted therapy[1]

Paclitaxel and trastuzumab is an effective regimen for stage I breast cancers with low rates of recurrence

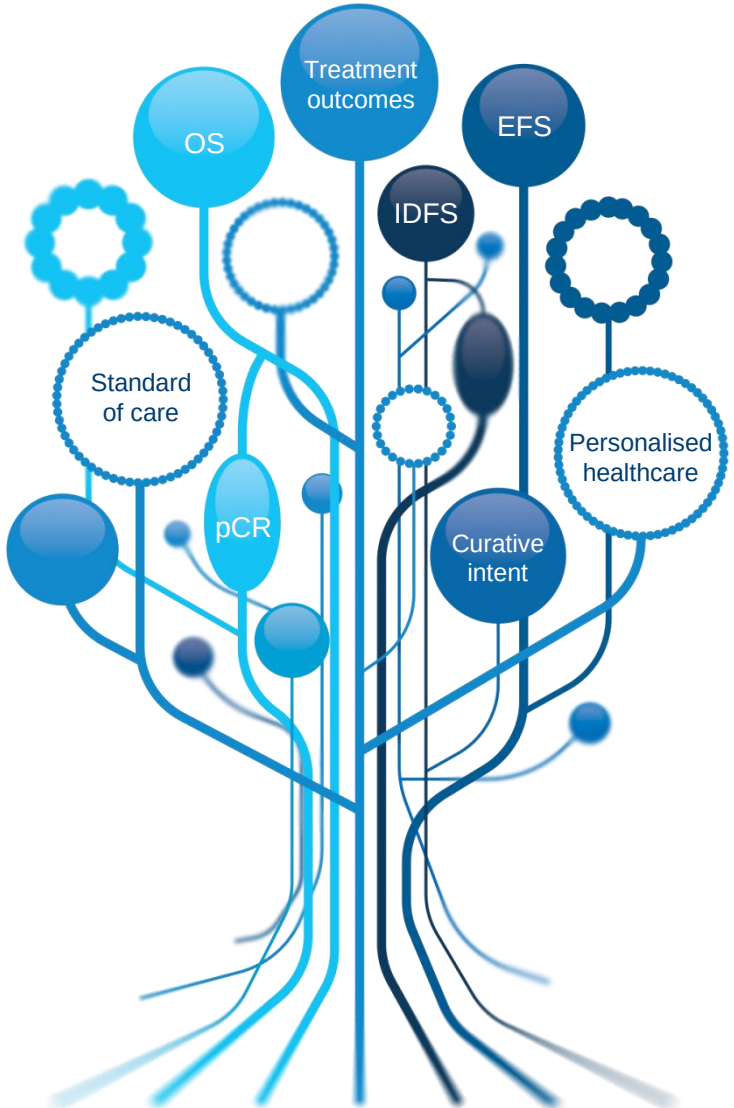
## Adjuvant systemic treatment[2]

Luminal B HER2-positive tumours are treated with chemotherapy, endocrine therapy and trastuzumab [I, A]*

No randomised data exist to support omission of chemotherapy in this group. However, in small, node-negative tumours, combination of single-agent paclitaxel and trastuzumab provides excellent results

* Level of evidence **I:** Evidence from at least one large, randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted, randomised trials without heterogeneity;
Grade of recommendation **A:** strong evidence for efficacy with a substantial clinical benefit, strongly recommended.

1. Curigliano G, *et al*. *Ann Oncol* 2017; **28**:1700–1712;
2. Senkus E, *et al*. *Ann Oncol* 2015; **26(Suppl. 5)**:v8–v30.

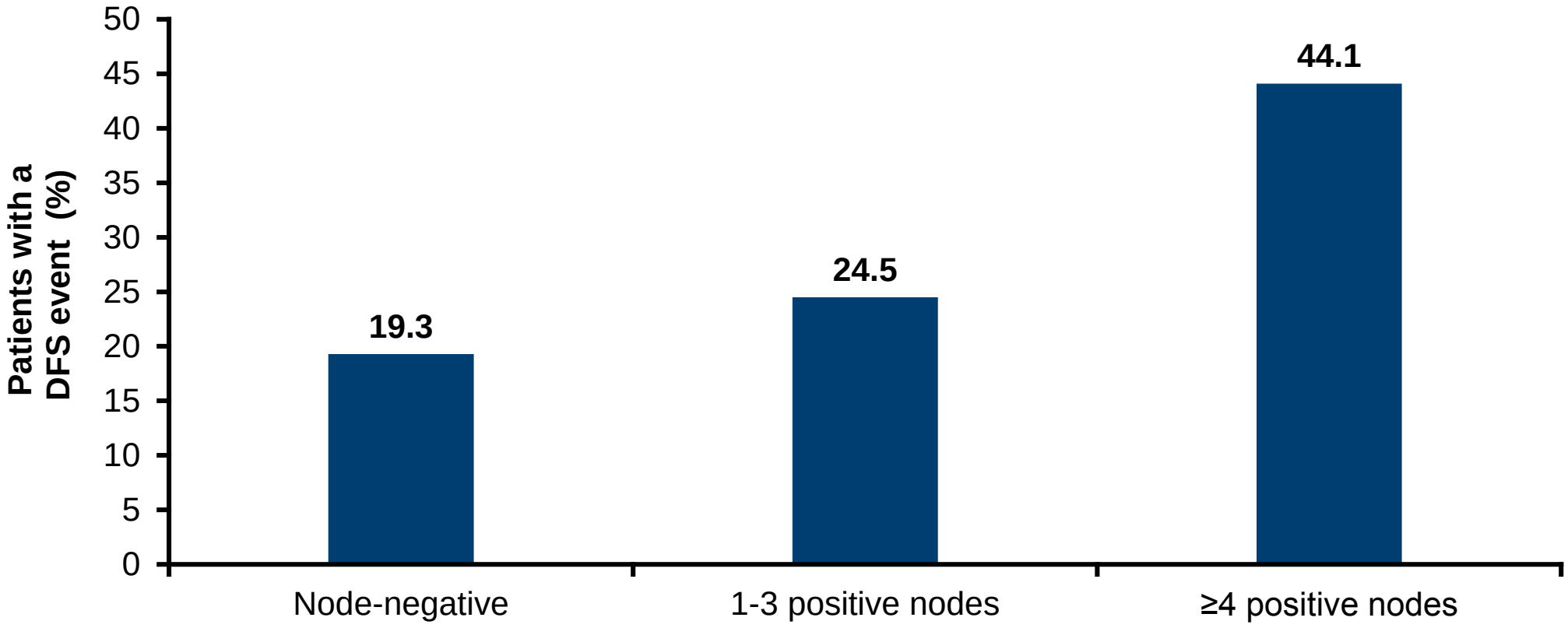



# How can higher-risk HER2-positive eBC patients be defined?

## *Nodal status*

# HERA: DFS event rate increases with increasing numbers of positive nodes

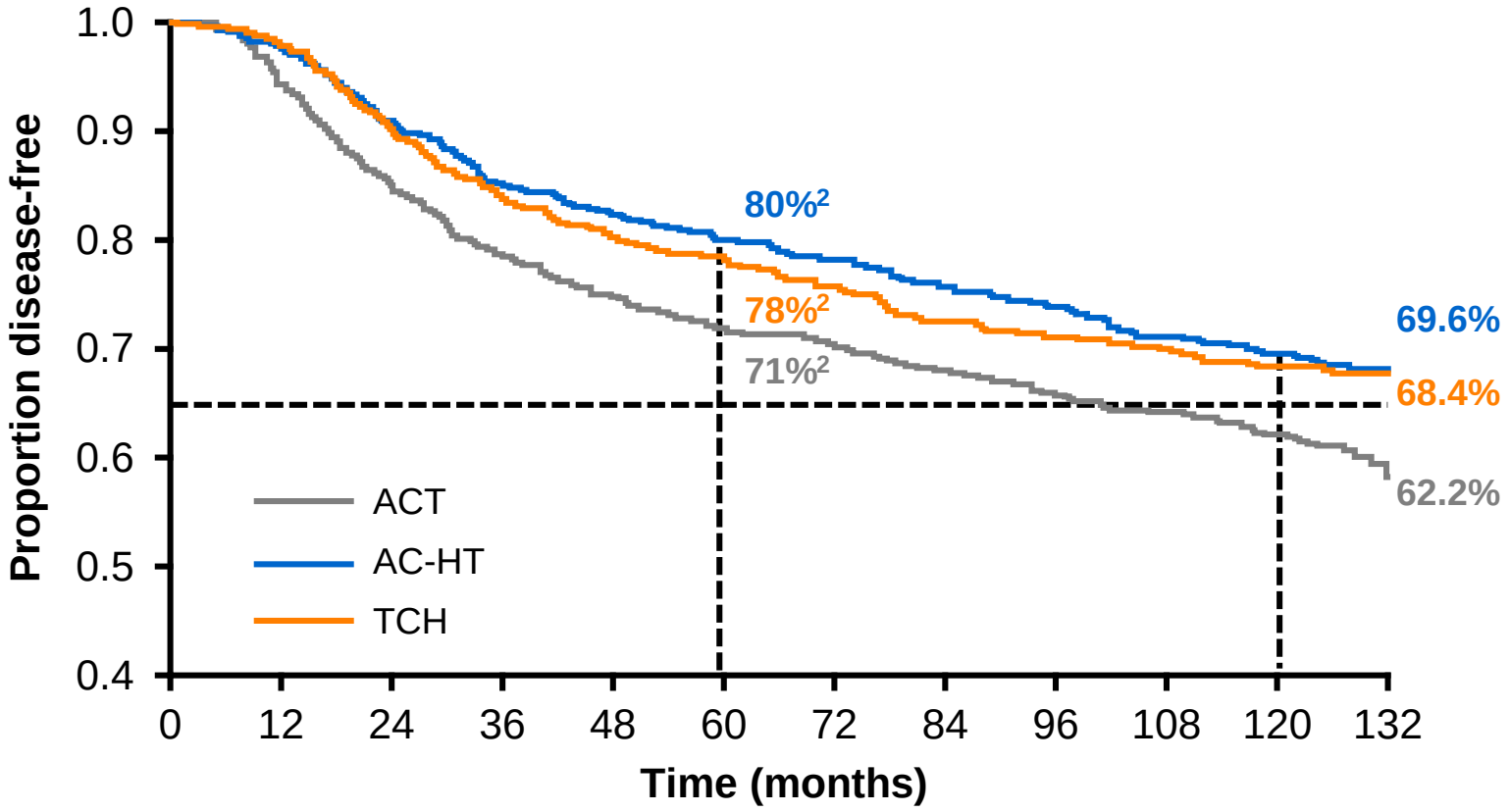
## HERA 11-year FU: DFS events by nodal status with 1 year of adjuvant trastuzumab




Cameron D, *et al. Lancet* 2017; **389**:1195–1205 (Supplementary information).

# BCIRG 006: Regardless of chemotherapy partner, after 1 year of adjuvant trastuzumab, ~30% of node-positive patients still relapse

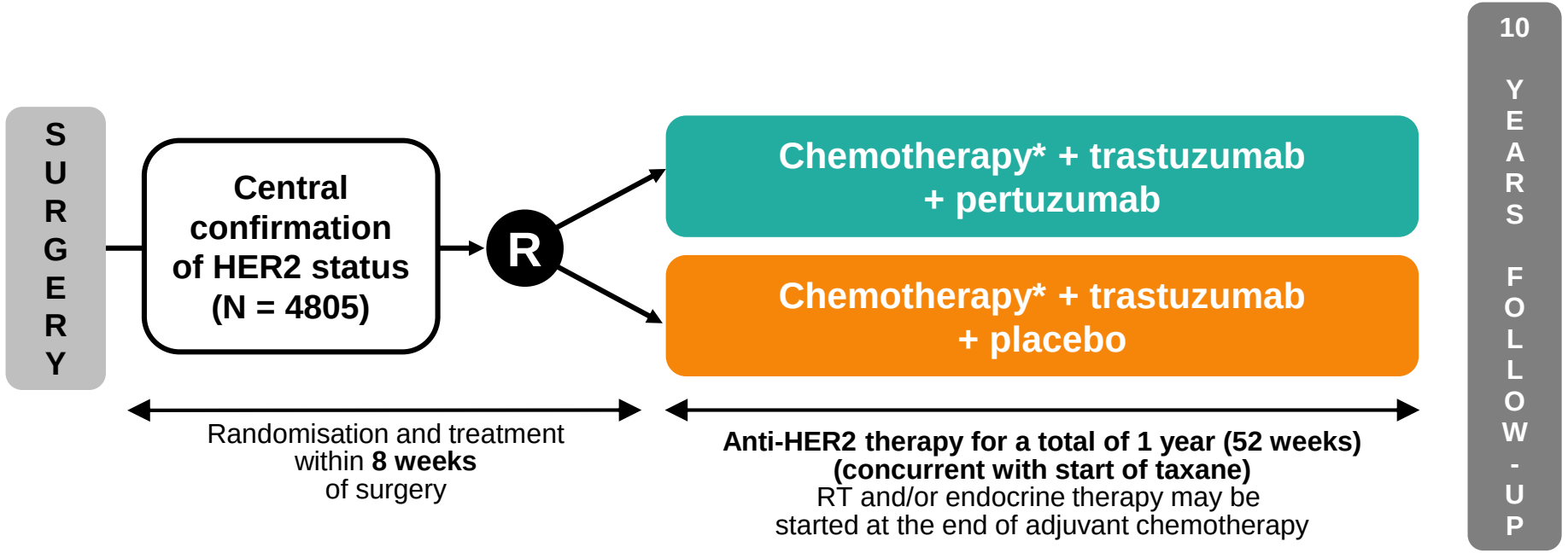
## BCIRG 006: DFS in node-positive disease after 10 years' follow-up[1]





1. Slamon D, *et al*. SABCS 2015 (Abstract S5-04; oral presentation);
2. Slamon D, *et al. N Engl J Med* 2011; **365**:1273–1283.

# APHINITY: Phase III study to assess pertuzumab plus trastuzumab in the adjuvant setting



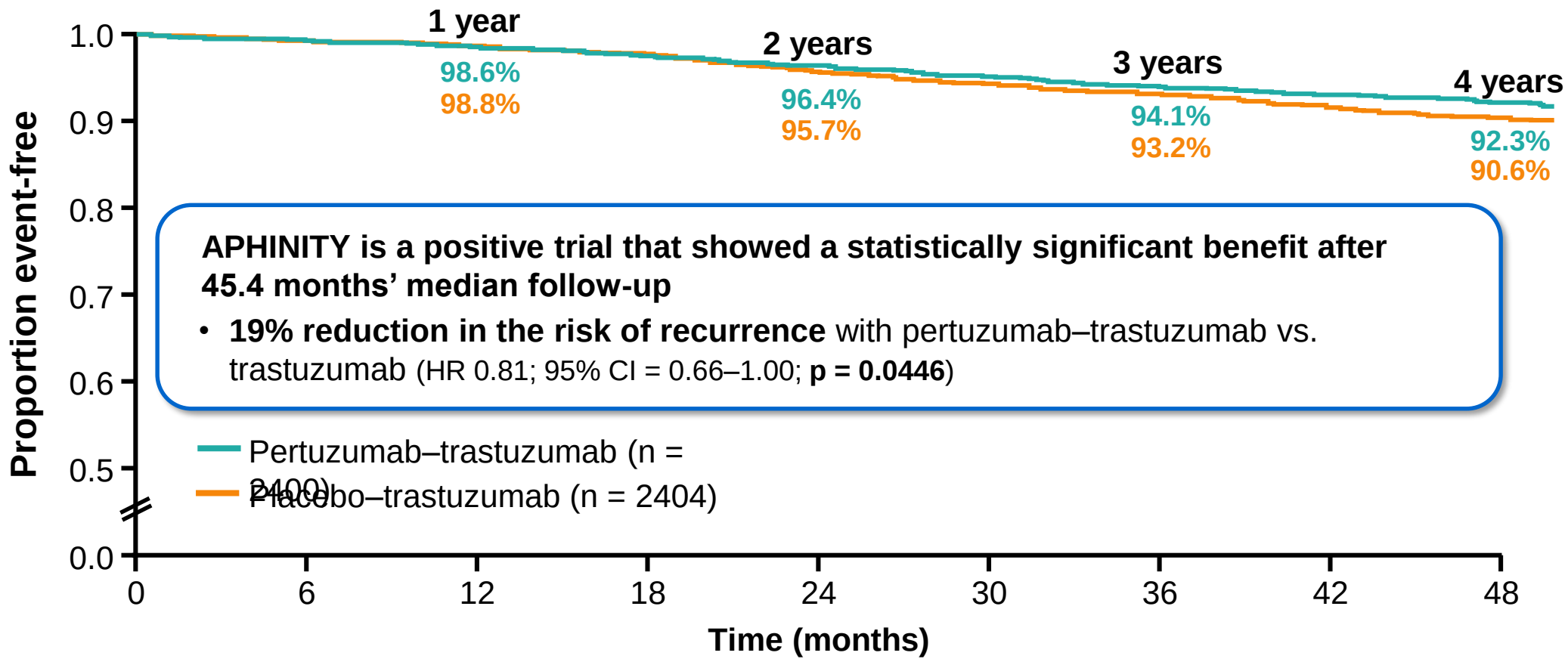

***** Standard anthracycline or non-anthracycline (TCH) regimens were allowed

- **Primary endpoint:** IDFS
- **Secondary endpoints:** IDFS with second non-breast primary cancers included, DFS, OS, RFI, DRFI, safety and HRQoL
- **Predefined stratification factors:** Chemotherapy regimen, HR status, nodal status, geographic region and protocol version (A vs. B)

DRFI, distant relapse-free interval; HRQoL, health-related quality of life; IDFS, invasive DFS; RFI, relapse-free interval.
*Pertuzumab is not yet approved in the adjuvant setting in Hong Kong

von Minckwitz G, *et al*. *N Engl J Med* 2017; **377**:122–131.

# APHINITY: Pertuzumab–trastuzumab plus chemotherapy significantly increased IDFS rates for HER2-positive eBC in the adjuvant setting




Stratification factors are: nodal status and protocol version, intended adjuvant chemotherapy and central hormone receptor status.
Hazard ratio was estimated by Cox regression.
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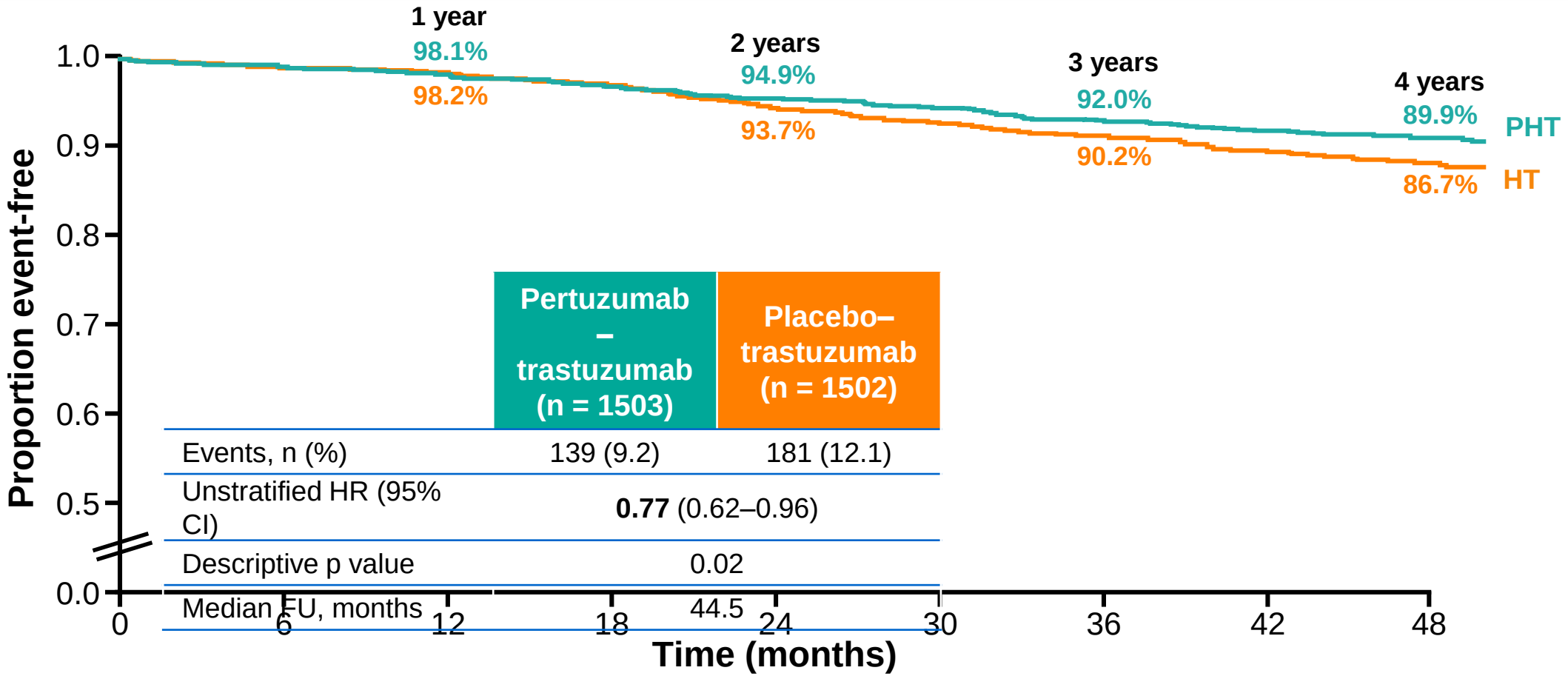
# APHINITY: Pertuzumab–trastuzumab significantly improved IDFS rates in HER2-positive, node-positive eBC in the adjuvant setting

## Lymph node-positive subgroup (n = 3005)

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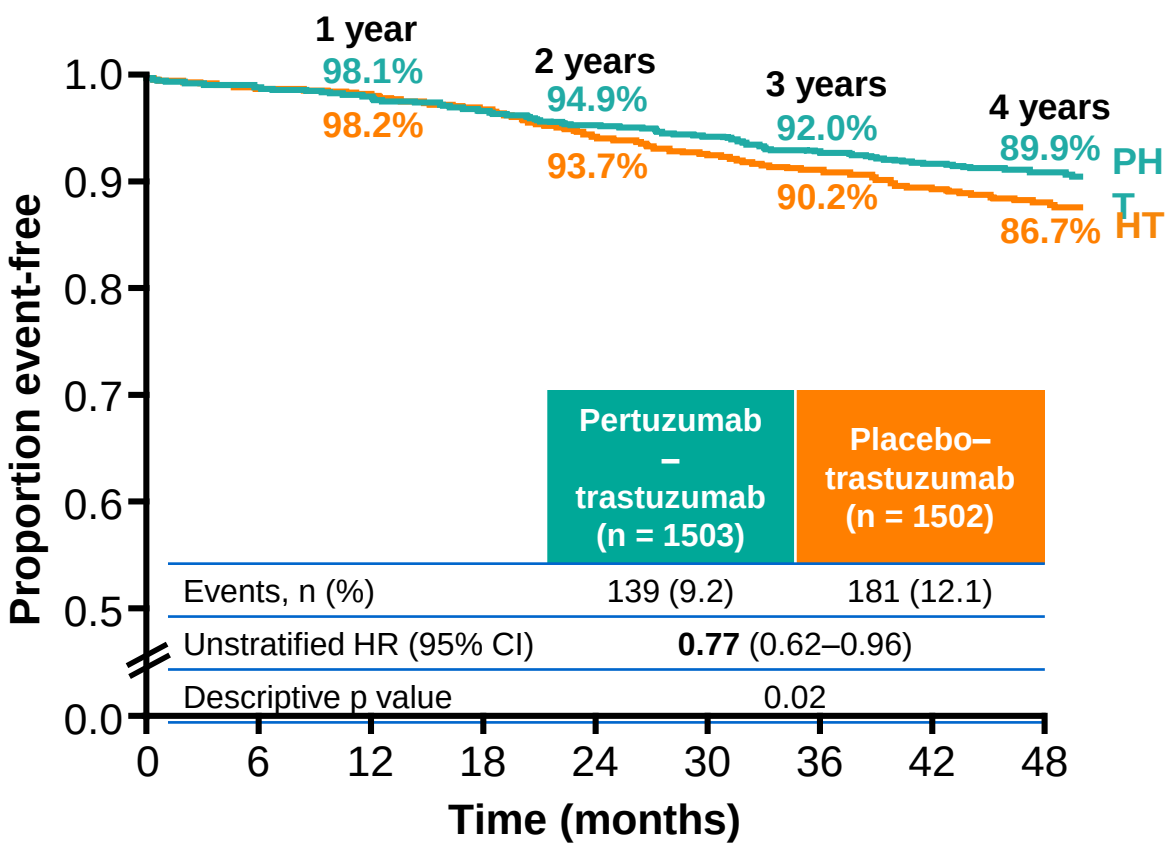
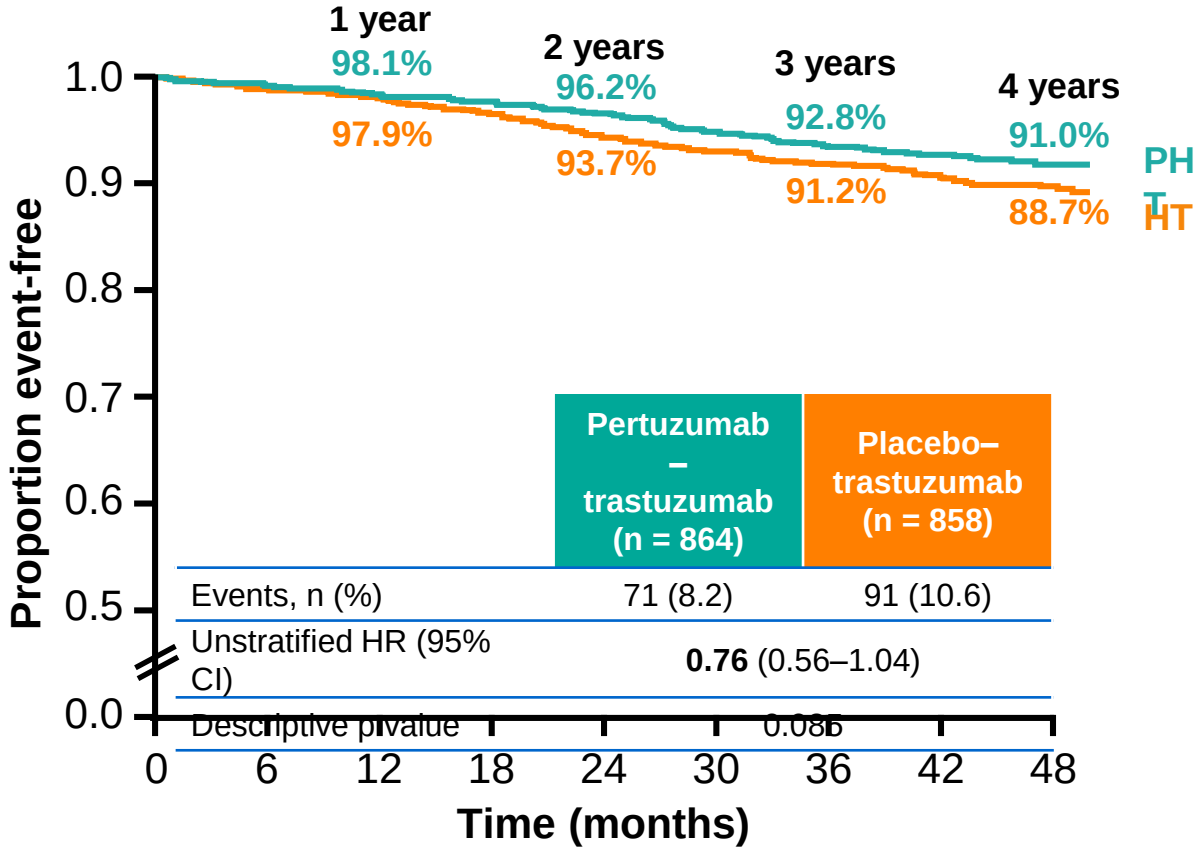
# APHINITY: The positive outcome of the study was likely driven by results in patients with disease at high risk of recurrence (e.g. N+ and/or HR-)

## Lymph node-positive subgroup (n = 3005)




## HR-negative subgroup (n = 1722)

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# APHINITY: Safety

| Event | Pertuzumab Group (N=2364) | Placebo Group (N=2405) |
|---|---|---|
| | *no. of patients (%)* | |
| Grade ≥3 adverse event | 1518 (64.2) | 1379 (57.3) |
| Neutropenia | 385 (16.3) | 377 (15.7) |
| Febrile neutropenia | 287 (12.1) | 266 (11.1) |
| Neutrophil count decreased | 228 (9.6) | 230 (9.6) |
| Diarrhea† | 232 (9.8) | 90 (3.7) |
| Anemia | 163 (6.9) | 113 (4.7) |
| Fatal adverse event‡ | 18 (0.8) | 20 (0.8) |
| Primary cardiac event§ | 17 (0.7) | 8 (0.3) |
| NYHA class III or IV heart failure and substantial decrease in LVEF¶ | 15 (0.6) | 6 (0.2) |
| Definite or probable cardiac death | 2 (0.1) | 2 (0.1) |
| Secondary cardiac event‖ | 64 (2.7) | 67 (2.8) |
| Identified automatically from LVEF assessments | 50 (2.1) | 47 (2.0) |
| Identified by cardiac advisory board | 14 (0.6) | 20 (0.8) |

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

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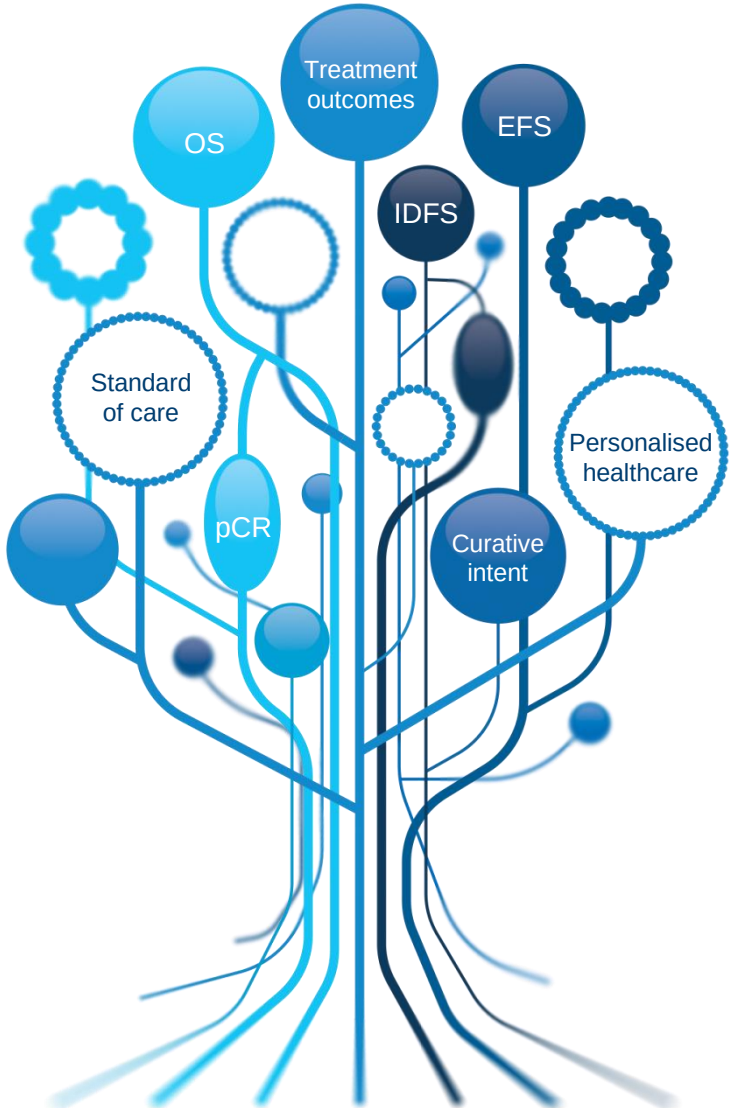
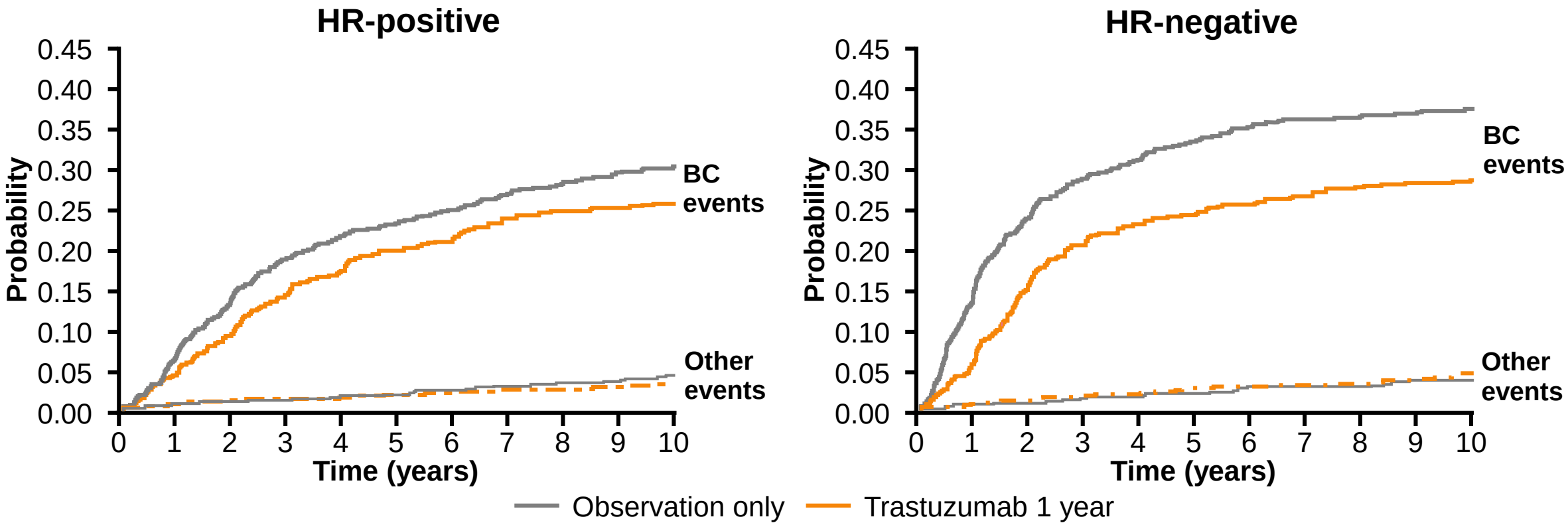



# How can higher-risk HER2-positive eBC patients be defined?

## *Hormone receptor status*

# HERA: HR-negative status confers a higher risk for early relapse, and within a shorter timeframe

## HERA 11-year FU: Cumulative incidence of type of DFS event with 1 year of adjuvant trastuzumab

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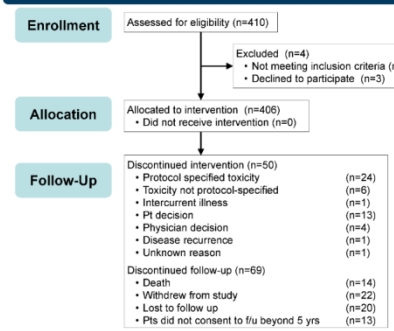


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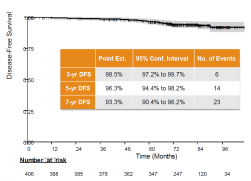
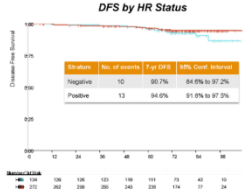



| | Point Est. | 95% Conf. Interval | No. of Events |
|---|---|---|---|
| 3-yr DFS | 98.5% | 97.2% to 99.7% | 6 |
| 5-yr DFS | 96.3% | 94.4% to 98.2% | 14 |
| 7-yr DFS | 93.3% | 90.4% to 96.2% | 23 |

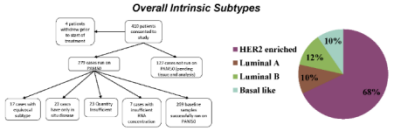
*DFS by HR Status*




| Stratum | No. of events | 7-yr DFS | 95% Conf. Interval |
|---|---|---|---|
| Negative | 10 | 90.7% | 84.6% to 97.2% |
| Positive | 13 | 94.6% | 91.8% to 97.5% |

### Intrinsic Subtypes & DFS

*Overall Intrinsic Subtypes*




*Subtype by HR Status*


*DFS Events by Intrinsic Subtype*

| | HER2 enriched | Luminal A | Luminal B | Basal like |
|---|---|---|---|---|
| Local/Regional Recurrence | 0 | 0 | 0 | 0 |
| New Contralateral Primary Breast Cancer | 2 | 0 | 0 | 0 |
| Distant Recurrence | 1 | 0 | 1 | 0 |
| Death | 4 | 1 | 1 | 1 |

### RESULTS: Secondary Outcomes

*Recurrence-Free Interval (RFI)*

| | Point Est. | 95% Conf. Interval | No. of Events |
|---|---|---|---|
| 3-yr RFI | 98.2% | 96.4% to >99.9% | 3 |
| 5-yr RFI | 96.1% | 94.0% to 98.3% | 7 |
| 7-yr RFI | 97.9% | 95.9% to 99.1% | 9 |

*Breast Cancer-Specific Survival (BCSS)*

| | Point Est. | 95% Conf. Interval | No. of Events |
|---|---|---|---|
| 3-yr BCSS | - | - | 0 |
| 5-yr BCSS | 99.7% | 99.1% to >99.9% | 1 |
| 7-yr BCSS | 98.8% | 97.0% to >99.9% | 3 |

*Overall Survival (OS)*

| | Point Est. | 95% Conf. Interval | No. of Events |
|---|---|---|---|
| 3-yr OS | 99.7% | 99.2% to >99.9% | 1 |
| 5-yr OS | 98.7% | 97.5% to 99.8% | 5 |
| 7-yr OS | 95.0% | 92.4% to 97.7% | 14 |

### DISCUSSION

- With a median follow-up of 6.5 years, the 7-year DFS was 93.3%, with just 4 distant recurrences.
- The 7-year RFI (including invasive local/regional + distant recurrences + deaths due to breast cancer) was 97.5%.
- Trend towards fewer recurrences in the HR+ patients (7-year DFS: 94.6% vs 90.7%).

### CONCLUSIONS

- These data suggest that TH as adjuvant therapy for node-negative HER2+ breast cancer is associated with few recurrences and only 4 distant recurrences with longer follow-up.
- Adjuvant TH is now a standard regimen for the majority of patients with stage I HER2+ breast cancer.

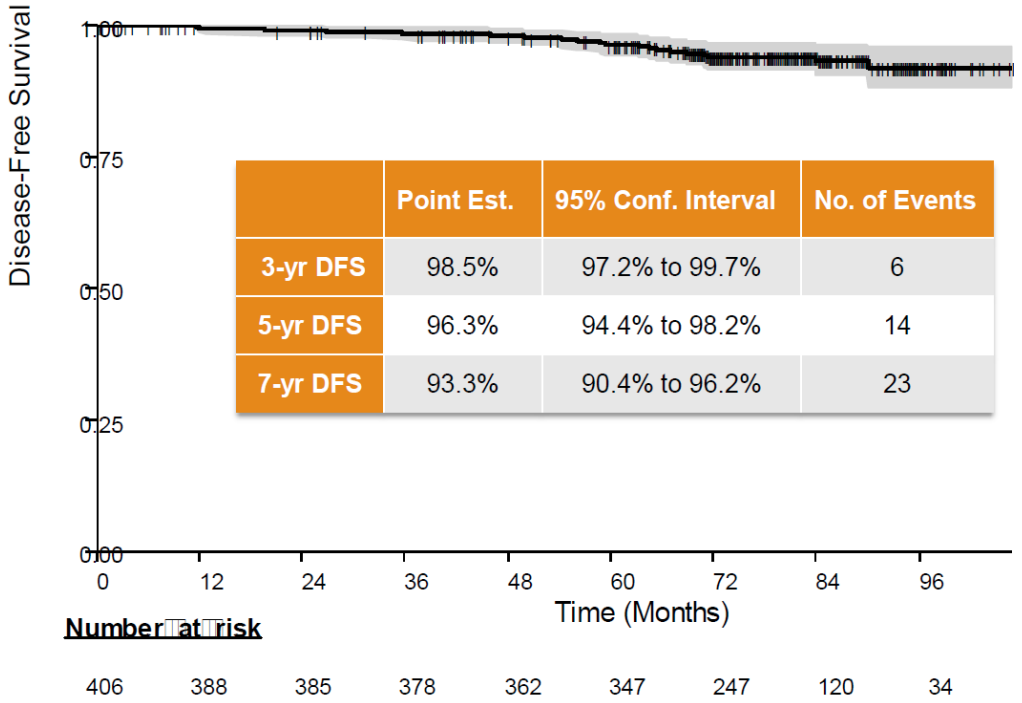
### REFERENCE

1. Tolaney. et al. Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer. NEJM. 2015;372:134-141.

Tolaney SM, *et al*. ASCO 2017 (Abstract 511; poster presentation).

# APT (Tolaney) trial: Trastuzumab plus paclitaxel is effective in the treatment of patients at low risk of recurrence

## Overall DFS



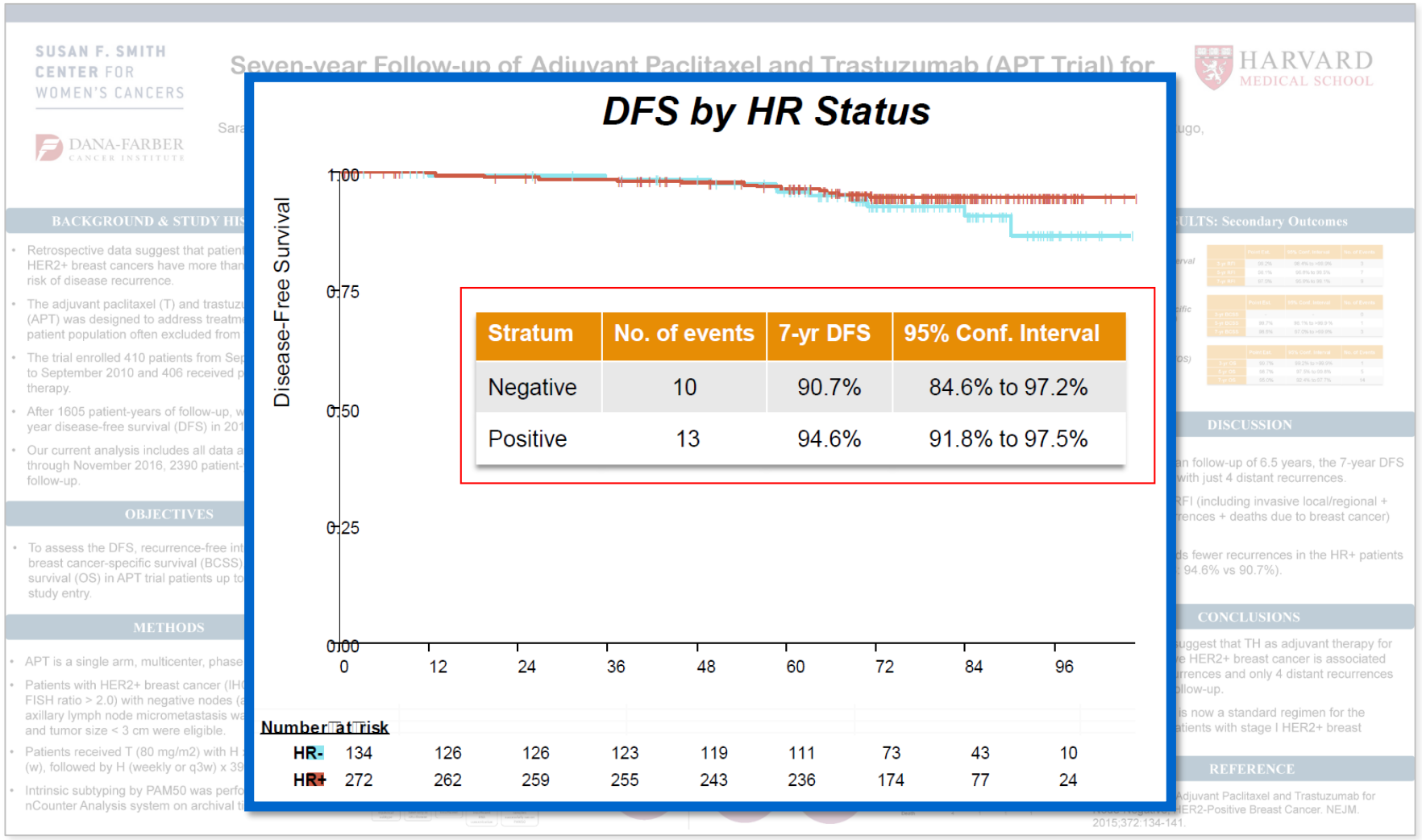

| | Point Est. | 95% Conf. Interval | No. of Events |
|---|---|---|---|
| 3-yr DFS | 98.5% | 97.2% to 99.7% | 6 |
| 5-yr DFS | 96.3% | 94.4% to 98.2% | 14 |
| 7-yr DFS | 93.3% | 90.4% to 96.2% | 23 |

## Patient Characteristics

| | | N | % |
|---|---|---|---|
| **Age** | | | |
| | <50 | 132 | 33 |
| | 50-70 | 233 | 57 |
| | ≥70 | 41 | 10 |
| **Size of Primary Tumor** | | | |
| T1a | ≤0.5 cm | 77 | 19 |
| T1b | >0.5 - ≤1.0 | 124 | 31 |
| T1c | >1.0 - ≤2.0 | 169 | 42 |
| T2 | >2.0 - ≤3.0 | 36 | 9 |
| **Histologic Grade** | | | |
| I | Well differentiated | 44 | 11 |
| II | Moderately differentiated | 131 | 32 |
| III | Poorly differentiated | 228 | 56 |
| **HR Status (ER and/or PR)** | | | |
| Positive | | 272 | 67 |
| Negative | | 134 | 33 |

Tolaney SM, *et al*. ASCO 2017 (Abstract 511; poster presentation).

# APT (Tolaney) trial: Small node-negative, HER2-positive tumours treated with 1 year of adjuvant trastuzumab are more likely to recur if HR-negative



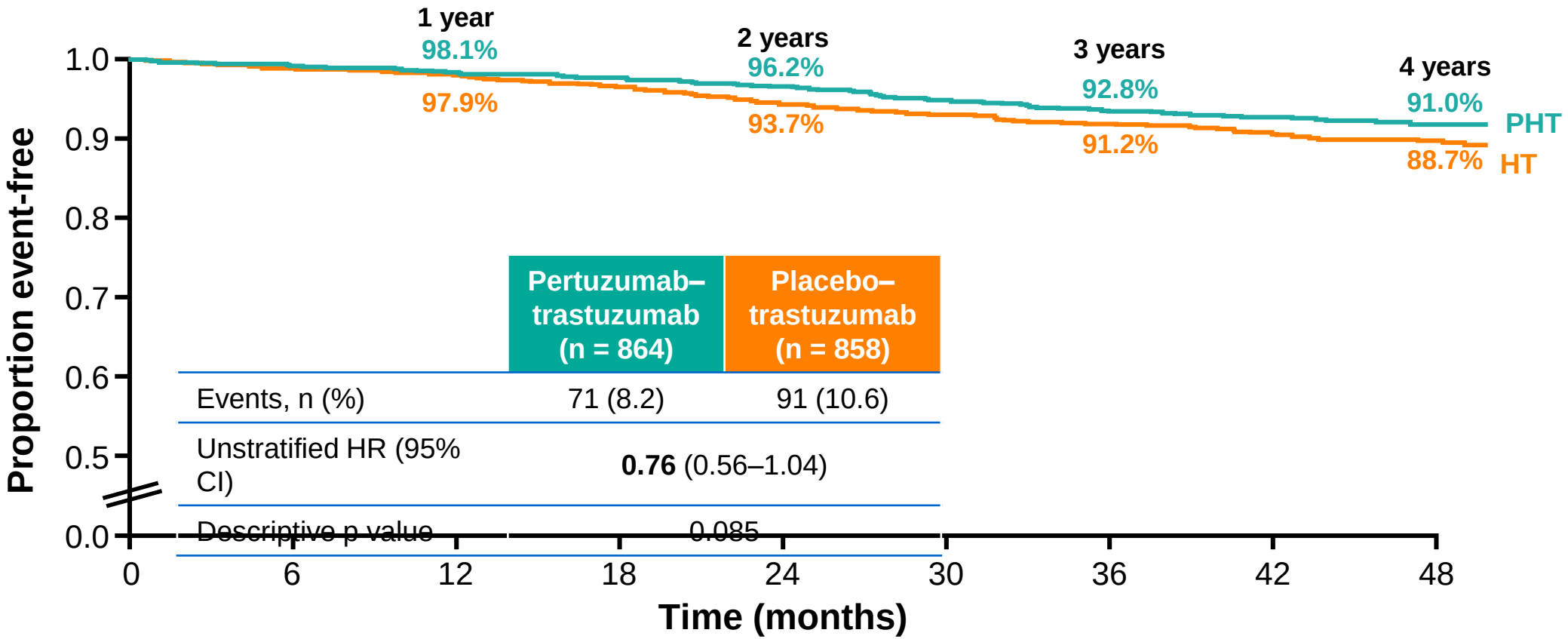

HR-positive

HR-negative

Tolaney SM, *et al*. ASCO 2017 (Abstract 511; poster presentation).

# APHINITY: IDFS rates in HER2-positive, HR-negative eBC with adjuvant pertuzumab–trastuzumab therapy

## HR-negative subgroup (n = 1722)

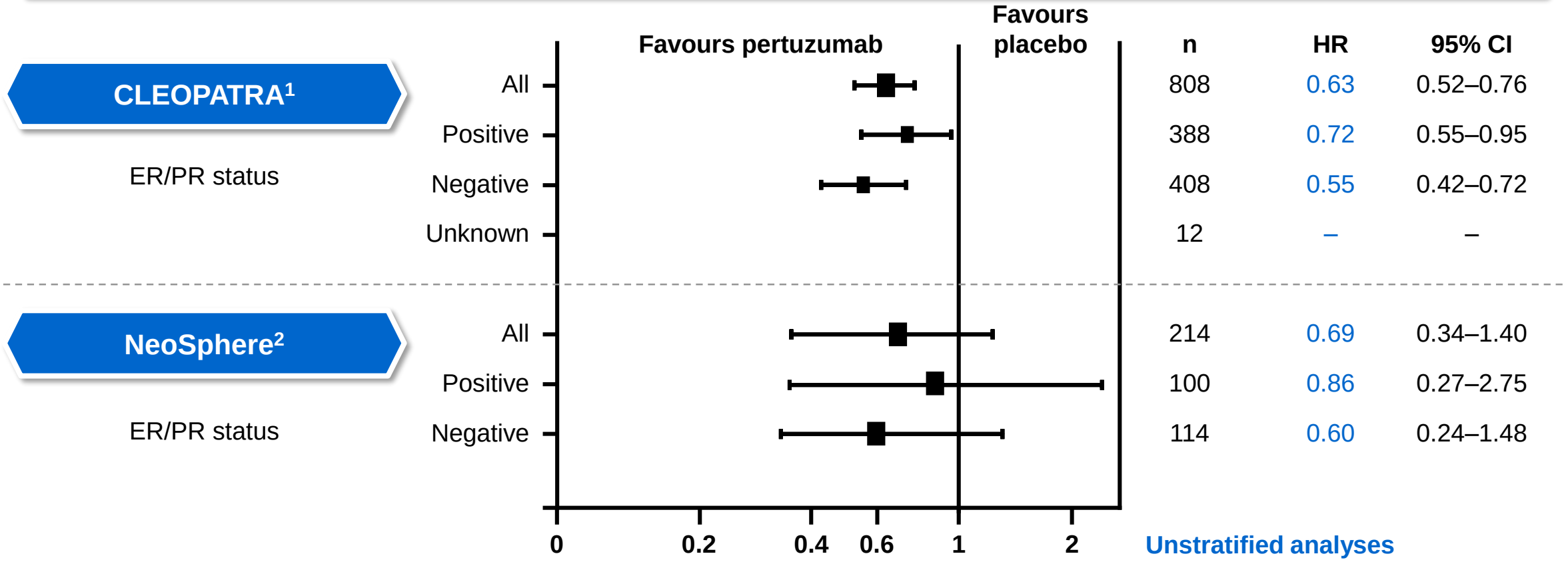



Hazard ratios were estimated by Cox regression.
*Pertuzumab is not yet approved in the adjuvant setting in Hong Kong

von Minckwitz G, *et al*. *N Engl J Med* 2017; **377**:122–131.

# Consistent efficacy benefit with pertuzumab–trastuzumab + chemotherapy in HER2-positive, HR-negative eBC & mBC

## PFS by HR status




mBC, metastatic breast cancer; PFS, progression-free survival.


1. Baselga J, *et al. N Engl J Med* 2012; **366**:109–119;
2. Gianni L, *et al. Lancet Oncol* 2016; **17**:791–800 (Supplementary information).

# International guidelines recommend the APHINITY regimen in patients with tumours at high risk of recurrence*

## St. Gallen Expert Consensus[1]

**Adjuvant systemic treatment recommendations:**

Dual blockade with pertuzumab and trastuzumab improves outcome among patients who are at **high risk of relapse due to lymph node involvement or hormone receptor negativity**

## NCCN Breast Cancer Guidelines[2]

**Adjuvant systemic treatment recommendations:**

If HER2-positive, **node-positive, HR-positive or HR-negative** receive adjuvant chemotherapy with trastuzumab ± pertuzumab (plus endocrine therapy if HR-positive)

ER, oestrogen receptor; NCCN, National Comprehensive Cancer Network.
* Pertuzumab is not yet approved in the adjuvant setting in Hong Kong

1. Curigliano G, *et al. Ann Oncol* 2017; **28**:1700–1712;
2. NCCN Breast Cancer Guidelines. Version 1, 2018

# Based on APHINITY, FDA label and NCCN guidelines support the continuation of pertuzumab–trastuzumab from neoadjuvant to adjuvant*

**Pertuzumab Prescribing Information[1]**

Following surgery, **patients should continue to receive PERJETA and trastuzumab to complete 1 year of treatment (up to 18 cycles)**

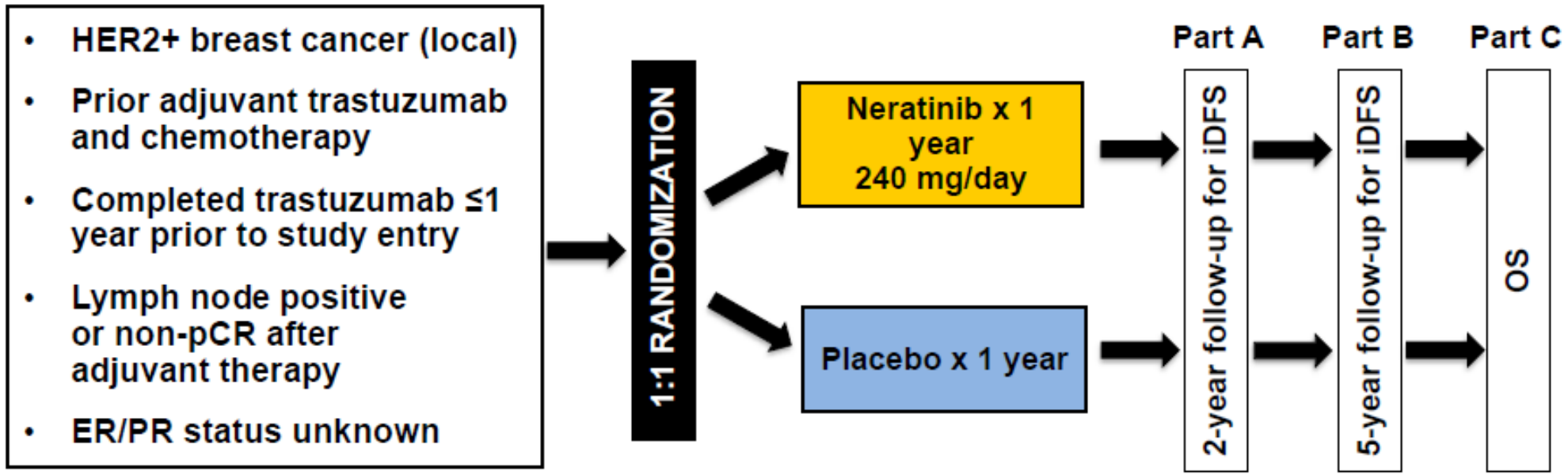
**NCCN Breast Cancer Guidelines[2]**

**Adjuvant systemic treatment recommendations after neoadjuvant therapy:**
If HER2-positive, complete up to one year of HER2-targeted therapy with trastuzumab ± pertuzumab in **node-positive, HR-positive or HR-negative tumours**
HER2-targeted therapy may be administered concurrently with radiation therapy and with endocrine therapy if indicated

* Pertuzumab is not yet approved in Hong Kong in the adjuvant setting

1. PERJETA (pertuzumab) Prescribing Information, 2017;
2. NCCN Breast Cancer Guidelines. Version 1, 2018.

# ExteNET: Final Study Design




Primary analysis: Invasive disease-free survival DFS (iDFS) in intent-to-treat (ITT) population (n = 2840)

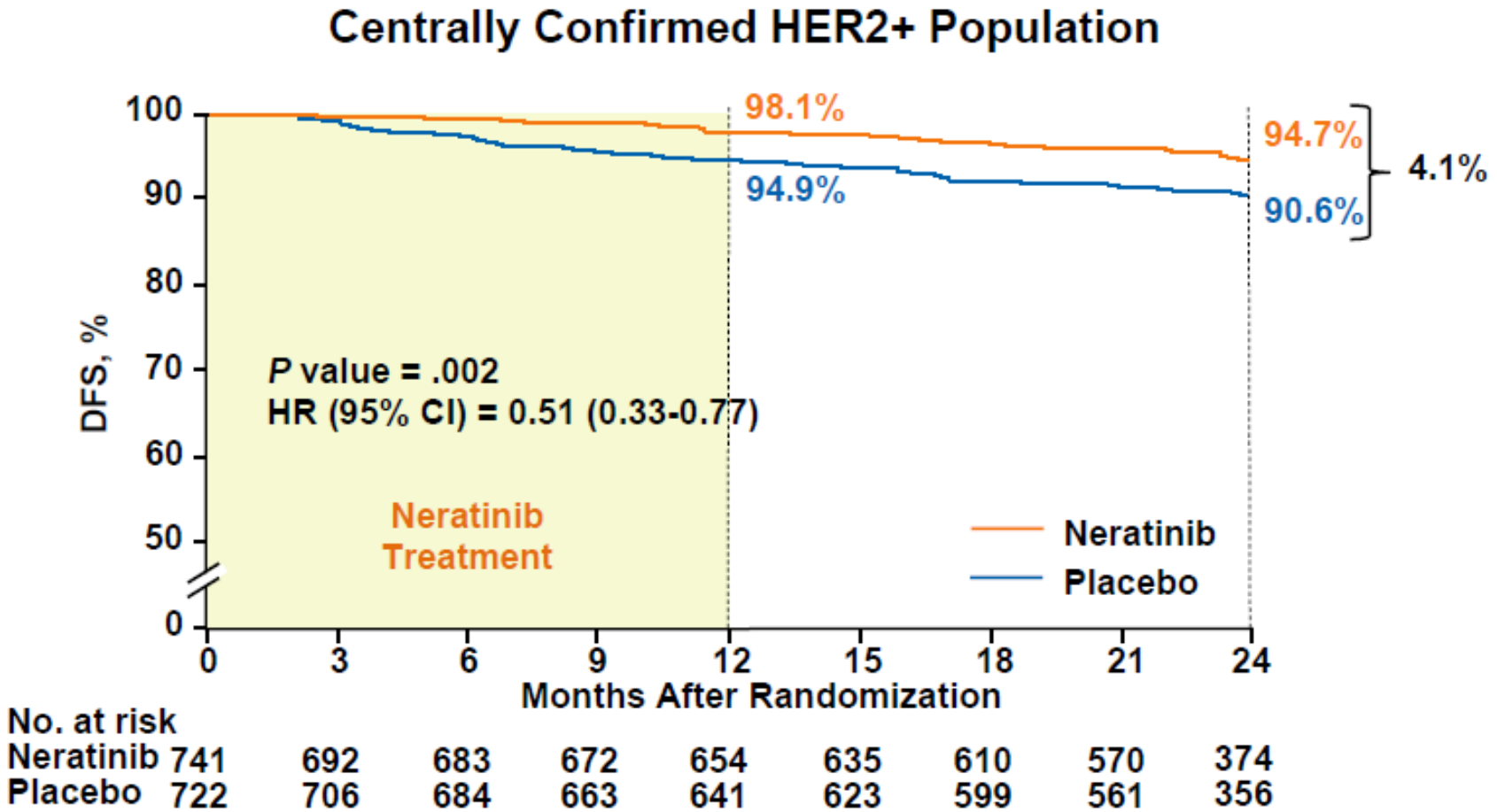
- iDFS at two years: HR = 0.67 (0.50-0.91); *P* = .009
  - HR positive (n = 1631, 57.4%); HR = 0.51; *P* = .001
  - Centrally confirmed HER2-positive 60% (n = 1463; 51%); HR = 0.51; *P* = .002

ER, estrogen receptor; OS, overall survival; pCR, pathological complete response; PR, progesterone receptor

Martin M, et al. *Lancet Oncol.* 2017;18(12):1688-1700. Chan A, et al. *Lancet Oncol.* 2016;17(3):367-377.

# Primary Analysis: iDFS in ccHER2+

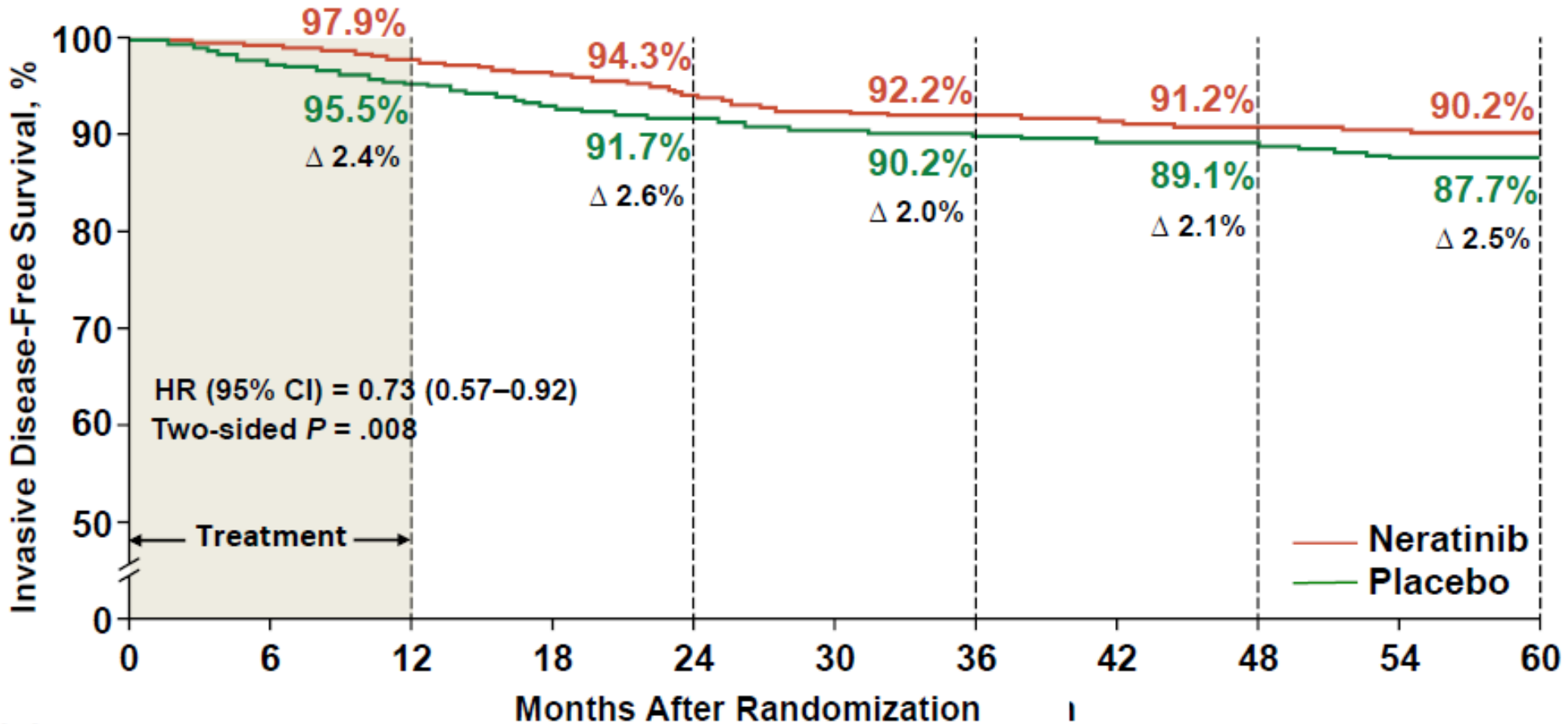
## Absolute benefit with neratinib in ccHER2+ population over 4%




ccHER2+, centrally confirmed HER2+

Chan A, et al. *Lancet Oncol*. 2016;17(3):367-377.

# ExteNET: 5-Year Analysis—iDFS




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Neratinib | 1420 | 1316 | 1272 | 1225 | 1106 | 978 | 965 | 949 | 938 | 920 | 885 |
| Placebo | 1420 | 1354 | 1298 | 1248 | 1142 | 1029 | 1011 | 991 | 978 | 958 | 927 |

Intention-to-treat population. Cut-off date: March 1, 2017

Martin M, et al. *Lancet Oncol.* 2017;18(12):1688-1700.

# 5-Year Analysis: By Endpoint

| Endpoint | Estimated Event-Free Rate, %[a] | | Hazard Ratio[b] (95% CI) | *P* Value[b] [2-Sided] |
|---|---|---|---|---|
| | Neratinib n = 1420 | Placebo n = 1420 | | |
| Invasive disease-free survival | 90.2 | 87.7 | 0.73 (0.57-0.92) | .008 |
| Disease-free survival with DCIS | 89.7 | 86.8 | 0.71 (0.56-0.89) | .004 |
| Distant disease-free survival | 91.6 | 89.9 | 0.78 (0.60-1.01) | .065 |
| Time to distant recurrence | 91.8 | 90.3 | 0.79 (0.60-1.03) | .078 |
| CNS recurrences | 1.30 | 1.82 | – | .333[c] |

Intention-to-treat population. Cut-off date: March 1, 2017

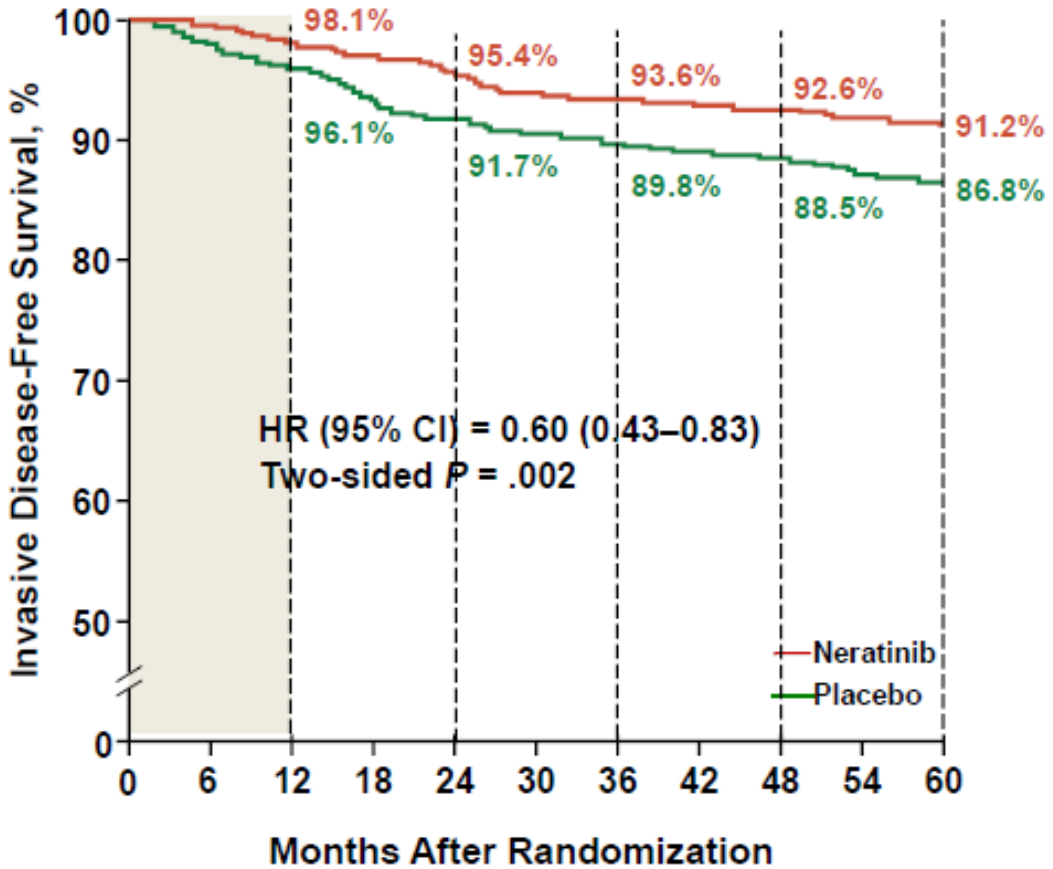
[a]Event-free rates for all endpoints, except CNS recurrences which is reported as cumulative incidence. [b]Stratified by randomization factors. [c]Gray's method

CNS, central nervous system; DCIS, ductal carcinoma *in situ*

Martin M, et al. *Lancet Oncol.* 2017;18(12):1688-1700.

# ExteNET: iDFS By Hormone Receptor Status

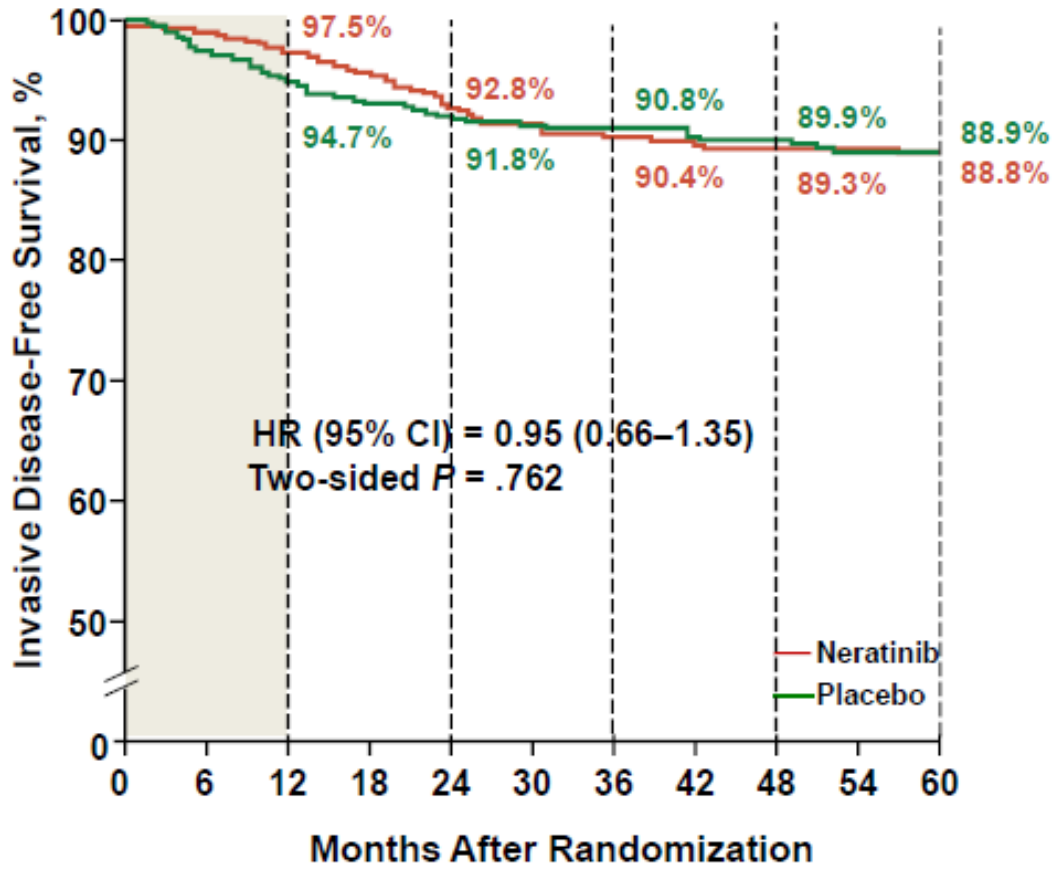
## HR-Positive Subgroup




No. at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Neratinib | 816 | 757 | 731 | 705 | 642 | 571 | 565 | 558 | 554 | 544 | 523 |
| Placebo | 815 | 779 | 750 | 719 | 647 | 581 | 567 | 556 | 551 | 542 | 525 |

## HR-Negative Subgroup




No. at risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Neratinib | 604 | 559 | 541 | 520 | 464 | 407 | 400 | 391 | 384 | 376 | 362 |
| Placebo | 605 | 575 | 548 | 529 | 495 | 448 | 444 | 435 | 427 | 416 | 402 |

Intention-to-treat population. Cut-off date: March 1, 2017

Martin M, et al. *Lancet Oncol.* 2017;18(12):1688-1700.

# ExteNET: Adverse Events (≥10% of Patients)

| | Neratinib n = 1408 | | | Placebo n = 1408 | | |
|---|---|---|---|---|---|---|
| n (%) | Grade 1-2 | Grade 3 | Grade 4 | Grade 1-2 | Grade 3 | Grade 4 |
| Diarrhea | 781 (55.5) | 561 (39.8) | 1 (0.1) | 476 (33.8) | 23 (1.6) | 0 |
| Nausea | 579 (41.1) | 26 (1.8) | 0 | 301 (21.4) | 2 (0.1) | 0 |
| Fatigue | 359 (25.5) | 23 (1.6) | 0 | 276 (19.6) | 6 (0.4) | 0 |
| Vomiting | 322 (22.9) | 47 (3.3) | 0 | 107 (7.6) | 5 (0.4) | 0 |
| Abdominal pain, general | 314 (22.3) | 24 (1.7) | 0 | 141 (10.0) | 3 (0.2) | 0 |
| Headache | 269 (19.1) | 8 (0.6) | 0 | 269 (19.1) | 6 (0.4) | 0 |
| Abdominal pain, upper | 201 (14.3) | 11 (0.8) | 0 | 93 (6.6) | 3 (0.2) | 0 |
| Rash | 205 (14.6) | 5 (0.4) | 0 | 100 (7.1) | 0 | 0 |
| Decreased appetite | 166 (11.8) | 3 (0.2) | 0 | 40 (2.8) | 0 | 0 |
| Muscle spasms | 157 (11.2) | 1 (0.1) | 0 | 44 (3.1) | 1 (0.1) | 0 |
| Dizziness | 143 (10.2) | 3 (0.2) | 0 | 125 (8.9) | 3 (0.2) | 0 |
| Arthralgia | 84 (6.0) | 2 (0.1) | 0 | 158 (11.2) | 4 (0.3) | 0 |

Antidiarrheal prophylaxis to minimize neratinib-related diarrhea was not protocol-mandated.

Chan A, et al. *Lancet Oncol.* 2016;17(3):367-377.

# Summary

- There remains a need to do more for patients with HER2-positive eBC as 1 in 4 patients experience recurrence or death after 18 cycles of trastuzumab (plus chemotherapy)[1]
- Risk factors are important in both predicting the prognosis of patients and in making treatment decisions[2]
- Patients with eBC at lower risk of recurrence, i.e. patients with stage I breast cancer, may be treated with single-agent trastuzumab and paclitaxel to reduce treatment burden[3]
- Recent data from the APHINITY trial demonstrated a significant improvement in IDFS rates for patients treated with pertuzumab–trastuzumab plus chemotherapy*[4]
  - At this time, patients with characteristics that increase the risk of recurrence, such as node-positive or HR-negative disease, appear to gain the most benefit from dual blockade with pertuzumab–trastuzumab in the adjuvant setting[4]
  - International guidelines have been updated to recommend the APHINITY regimen in patients with tumours at high risk of recurrence[5–7]

1. Slamon D, *et al*. SABCS 2015 (Abstract S5-04; oral presentation); 2. Cortazar P, *et al*. *Lancet* 2014; **384**:164–172;
3. Tolaney SM, *et al*. *N Engl J Med* 2015; **372**:134–141; 4. von Minckwitz G, *et al*. *N Engl J Med* 2017; **377**:122–131;
5. Curigliano G, *et al*. *Ann Oncol* 2017; **28**:1700–1712;
6. NCCN Breast Cancer Guidelines. Version 4, 2017 – February 7, 2018;
7. Cherny NI, *et al*. *Ann Oncol* 2015; **26**:1547–1573.

* Pertuzumab is not yet approved in Hong Kong in the adjuvant setting

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*2018 ASCO Annual Meeting*

# Less is more : Opportunities (… challenges ?) to de-escalate therapy

**Martine Piccart, MD, PhD**

***with the help of Noam Ponde, Matteo Lambertini, Rafael Caparica, Mariana Brandao… and Richard Gelber***

**Institut Jules Bordet**
**Université Libre de Bruxelles (U.L.B.)**

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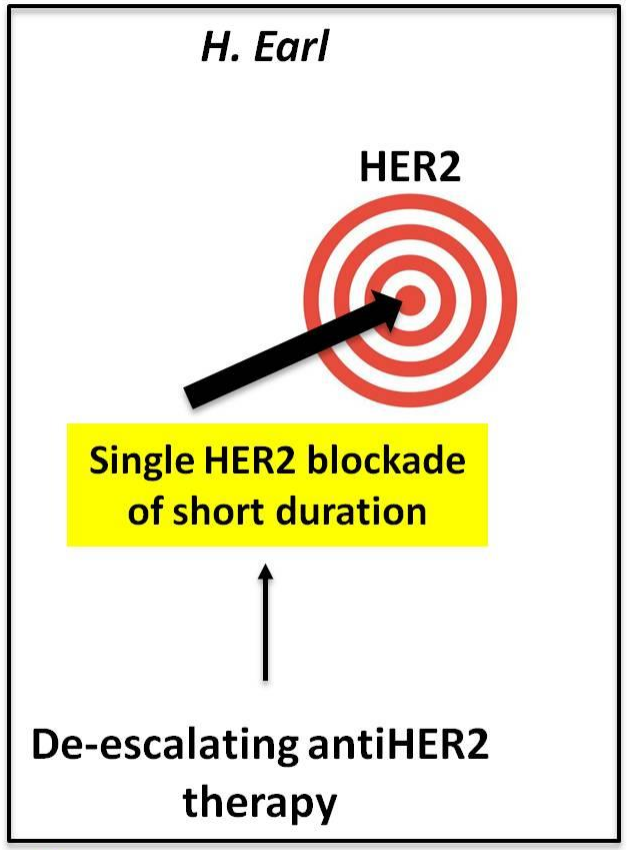


- Persephone compared to other trials exploring shorter adjuvant trastuzumab durations
- Strengths/weaknesses of Persephone
- Should we change clinical practice tomorrow ?

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*(3) NHS/UK, abst 508*

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# Trials of 6 months versus 12 months of Adjuvant Trastuzumab

| Trial/Sample | Recruitment Time | Timing of randomization | Patient characteristics | Chemotherapy | | Prespecified non inferiority margin | Results |
|---|---|---|---|---|---|---|---|
| | | | | % A and T | % concomitant trastuzumab | | |
| **6 months vs 12 months** | | | | | | | |
| PHARE (1)<br>N = 3380 | 6 y | at 6 m | N- 55%<br>ER+ 58% | 74% | 56% | 1.15 | DFS events at 2 y<br>8.9% vs 6.2%<br>HR 1.28 (1.05-1.56) |
| HORG (2)<br>N = 481 | 8 y | upfront | N- 21%<br>ER+ 67% | 100% | 100% | 1.53 | DFS events at 3 y<br>6.7% vs 4.3%<br>HR 1.57 (0.86-2.10) |
| PERSEPHONE (3)<br>N = 4089 | 8 y | within first 6 m | N- 59%<br>ER+ 69% | 48% | 47% | 1.29 | DFS events at 4 y<br>11.6% vs 11.2%<br>HR 1.07 (0.93-1.24) |

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*1. Pivot X el al Lancet Oncol 2013; 2. Mavroudis D et al Annals of Oncol 2015; 3. Earl HM et al ASCO 2018*

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# Trials of Shorter Durations of Adjuvant Trastuzumab

| Trial | Sample | Recruitment Time | Timing of randomization | Patient characteristics | Chemotherapy | | Prespecified non inferiority margin | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | % A and T | % concomitant trastuzumab | | |
| **6 months vs 12 months** | | | | | | | | |
| PHARE (1) | 3380 | 6 y | at 6 m | N- 55%<br>ER+ 58% | 74% | 56% | 1.15 | DFS events at 2 y<br>8.9% vs 6.2%<br>HR 1.28 (1.05-1.56) |
| HORG (2) | 481 | 8 y | upfront | N- 21%<br>ER+ 67% | 100% | 100% | 1.53 | DFS events at 3 y<br>6.7% vs 4.3%<br>HR 1.57 (0.86-2.10) |
| PERSEPHONE (3) | 4089 | 8 y | within first 6 m | N- 59%<br>ER+ 69% | 48% | 47% | 1.29 | DFS events at 4 y<br>11.6% vs 11.2%<br>HR 1.07 (0.93-1.24) |
| **9 weeks vs 12 months** | | | | | | | | |
| SHORT-HER (4) | 1253 | 9 y | upfront | N- 53%<br>ER+ 68% | 100% | 100% | 1.29 | DFS events at 5 y<br>14.6% vs 12.5%<br>HR= 1.15 (90% CI 0.91-1.46) |
| SOLD (5) | 2176 | 9 y | upfront | N- 60%<br>ER+ 66% | 100% | 100% | 1.3 | DFS events at 5 y<br>12% vs 9.5%<br>HR 1,39 (90% CI 1.12-1.72) |

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*1. Pivot X el al Lancet Oncol 2013; 2. Mavroudis D et al Annals of Oncol 2015; 3. Earl HM et al ASCO 2018; 4. Earl HM et al ASCO 2018; 5. Conte PF et al ASCO 2017*

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Presented By Martine Piccart-Gebhart at 2018 ASCO Annual Meeting

# Non-inferiority trials : when and how ?

- *Is there a justification for running a non-inferiority trial in the first place ?*
- *Does the selected non-inferiority margin make sense ?*

- Trastuzumab < 12 m : Yes !
  - cheaper, more convenient, less cardiotoxic…
- What is the largest loss of effect that is clinically acceptable ?

  -> Persephone : ≤ 3% absolute ↓ in DFS with 80% DFS assumed for 12 m trast at 4y)

  -> FDA : must be « *much smaller* » than th benefit of the active control over placebo…
  BCIRG-006 : 7 to 9% benefit of trastuzumab 12 m at 4y follow-up

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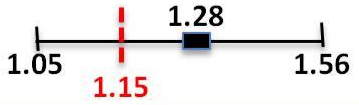
# Selection of the “non inferiority margin”

**Phare**

- Focus on Hazard Ratio (HR) and an acceptable ↑ in relative risk of a DFS event
- HR must show an upper boundary of the 95% CI < 1.15 indepe… from the actual DFS %

**Would patients accept 2-3% absolute reductions in DFS at 4y in return for the benefits of a shorter trastuzumab duration ?**

*Non inferiority claim NOT supported by trial results*




**Persephone**

- Fe… …ptable absolute … at 4y … …ence set at 3% max… then HR non inferiority margin established taking into account the actual DFS % observed

*Observed 4y DFS 89,8% instead of estimated 80% -> HR non inferiority margin changed from 1,17 to 1,31*

*Non inferiority claim supported by trial results*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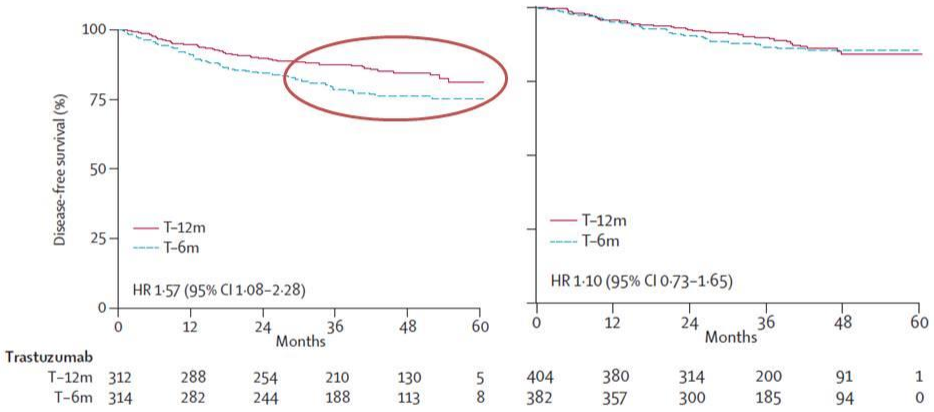
# HER2+ HR- disease : other “signals” that longer trastuzumab could be better than shorter trastuzumab

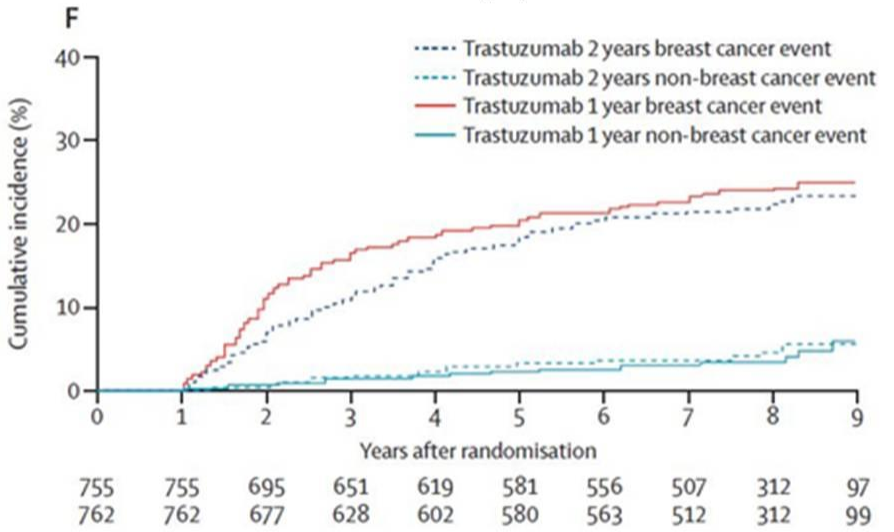
## Phare (1)




**Sequential CT-T** Concomitant CT-T

**HR negative: Trastuzumab 6 months <u>much worse</u> in the <u>sequential CT-T arm</u>**

## Hera (2)




**Suggestion of a transient benefit from continuing trastuzumab after 1 y in HR- subgroup**

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*1. Pivot X el al Lancet Oncol 2013; 2. Goldhirsch et al The Lancet 2013*

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# Cardiotoxicity in trials of 6 months versus 12 months of trastuzumab

| | Sample | Timing of randomization | % receiving anthracyclines | | LEVF monitoring | Cardiac events Shorter vs longer trastuzumab |
|---|---|---|---|---|---|---|
| PHARE (1) | 3384 | At 6 months* | | | q3m for 2y then q6m | 1.9% vs 5.7% |
| HORG (2) | 481 | | | 100% | q3m until end of treatment | 0 vs 2 cases |
| PERSEPHONE (3) | 2430/ | line up to the 9th cycle of trastuzumab | 90% | 47% | q3m until end of treatment | 9% vs 12% |

**Less « cardiotoxicity » with shorter trastuzumab duration in all trials !**

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*1. Pivot X el al Lancet Oncol 2013; 2. Mavroudis D et al Annals of Oncol 2015; 3. Earl HM et al British J of Cancer 2016*

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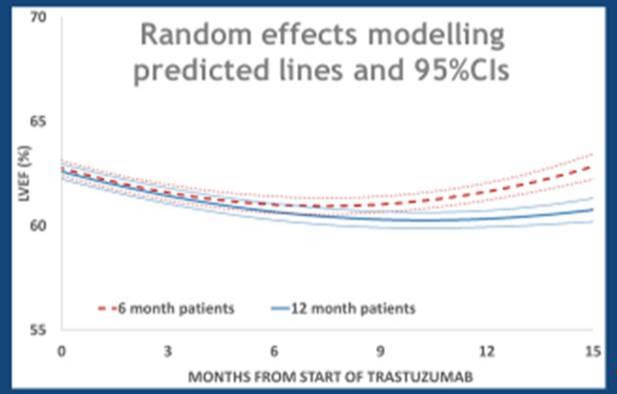
# Are we really concerned by cardiotoxicity ?

## Random effects modelling of LVEFs

- The quadratic change over time proves that cardiac function recovers post-trastuzumab (p<0.0001)
- 6-month patients had a more rapid recovery (p=0.02)




Ref: Earl et al. British Journal of Cancer (2016) 115, 1462–1470

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: 25

**Earlier « recovery » in the 6 month arm… ???**

- **Only 1 post treatment assessment in the 12 m arm**
- **At least 2 more points (18 m – 21 m) needed for a fair comparison**

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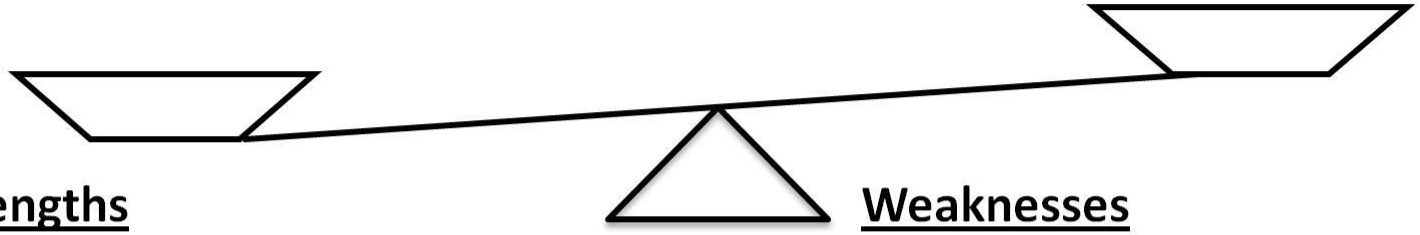
Presented By Martine Piccart-Gebhart at 2018 ASCO Annual Meeting

# Persephone : strengths and weaknesses



## Strengths

- Highly relevant question in 2007
- Very large, nationwide, government supported trial
- Pragmatic
- Excellent treatment compliance (> 82%)
- Careful cardiac monitoring
- Quality of life collected
- Health technology assessment pending
- Carefully planned interim analyses (n = 3) for futility

## Weaknesses

- Somewhat less relevant question today except for low income countries
- Persephone population not representative of today's populations (sequential T has ↓↓, more A+T use in high risk or T alone in low risk patients)
- Potential biases with the randomization « window » of 6 m…; landmark analysis, however, somewhat reassuring

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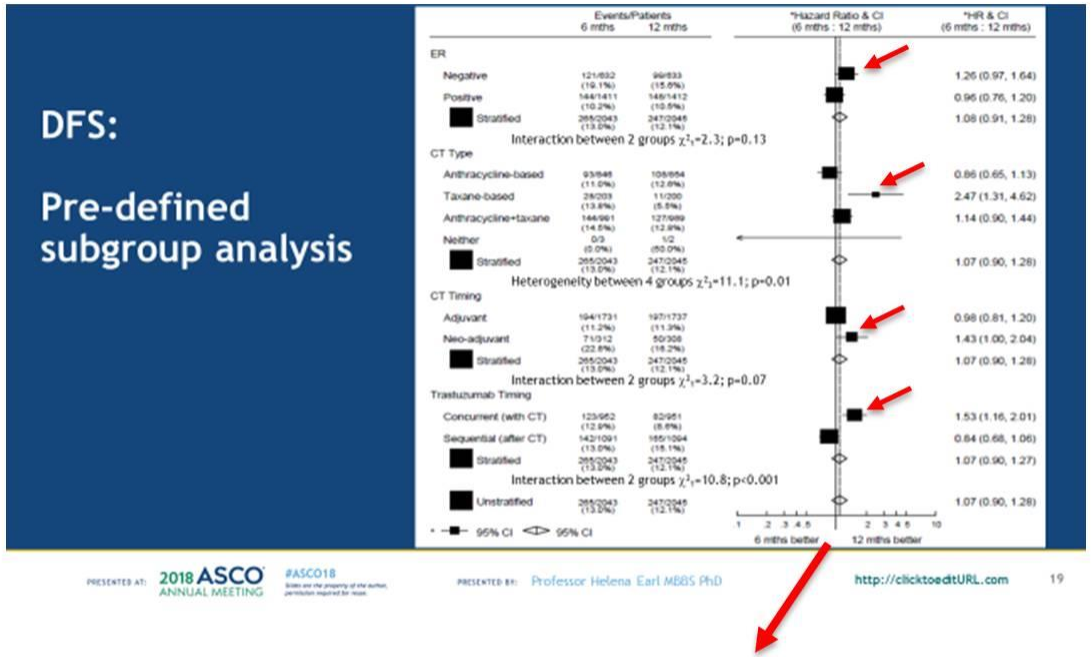
# Why I will not change my clinical practice tomorrow




**Subgroups for which 12 m might be superior**

- **ER-**
- **Taxane w/o Anthracycline**
- **Neoadjuvant CTX use**
- **Concomitant CTX – trastuzumab administration**

**Further work needed to reliably identify subgroups for which shorter trastuzumab therapy could become « standard » of care (? Combined efforts with Phare investigators)**

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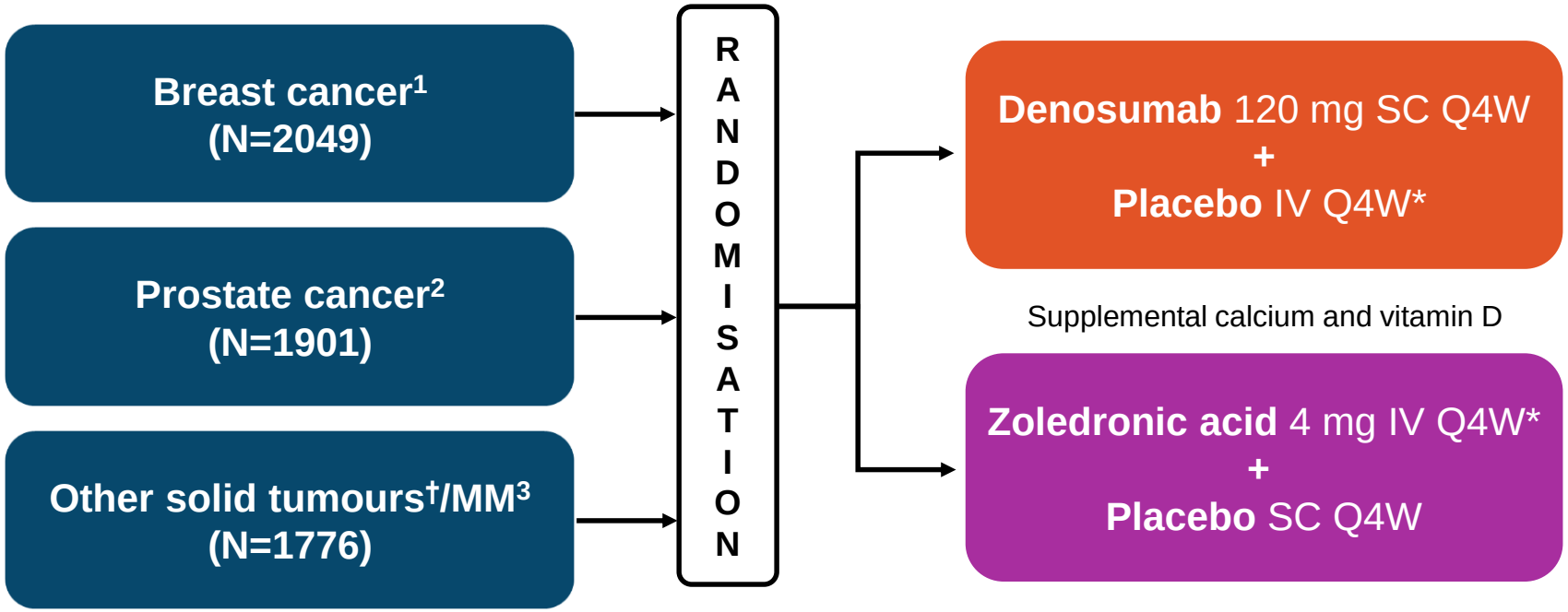
# Breast cancer is common for bone metastases

| Cancer | Prevalence,* thousands[1] | Incidence of bone metastases, %[2] | Median survival after developing bone metastases, months[2–4] |
|---|---|---|---|
| Breast | 5189 | 65–75 | 20–24 |
| Prostate | 3200 | 65–75 | 12–53 |
| Lung | 1677 | 30–40 | 3–6 |
| Bladder | 1172 | 40 | 7 |

1. GLOBOCAN 2008. Available from www.globocan.iarc.fr (accessed January 2013);
2. Coleman RE. Cancer Treat Rev 2001;27:165–76;
3. Coleman RE. Cancer 1997;80:1588–94;
4. Otto T, et al. Urology 2001;57:55–9.

*Worldwide 5-year prevalence.

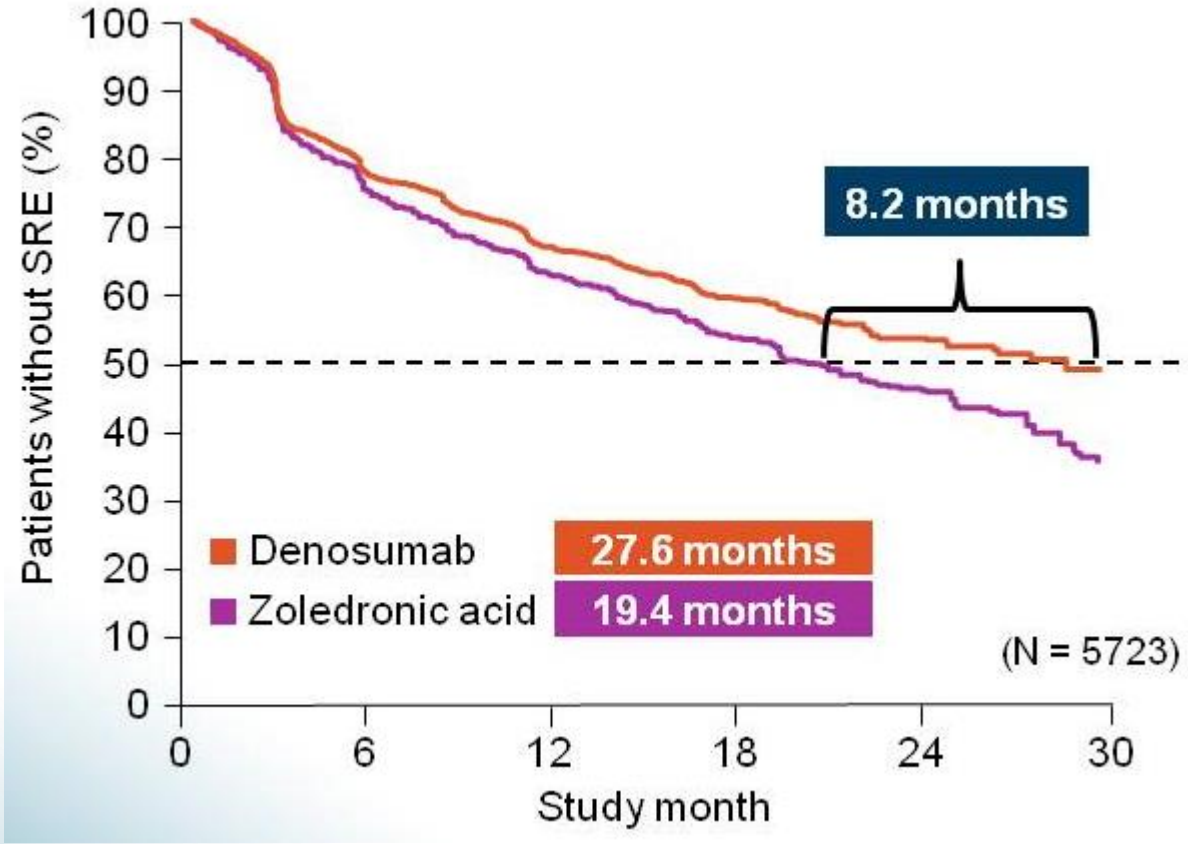
# Pivotal Phase III bone metastases trials with denosumab: three trials of identical design in different patient populations




1. Stopeck AT, et al. J Clin Oncol 2010;28:5132–9;
2. Fizazi K, et al. Lancet 2011;377:813–22;
3. Henry DH, et al. J Clin Oncol 2011;29:1125–32.

*Per protocol and zoledronic acid label, IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine.
†Excluding breast and prostate.
IV, intravenously; MM, multiple myeloma; Q4W, every 4 weeks; SC, subcutaneously.

# Significantly longer time without an SRE with denosumab vs zoledronic acid



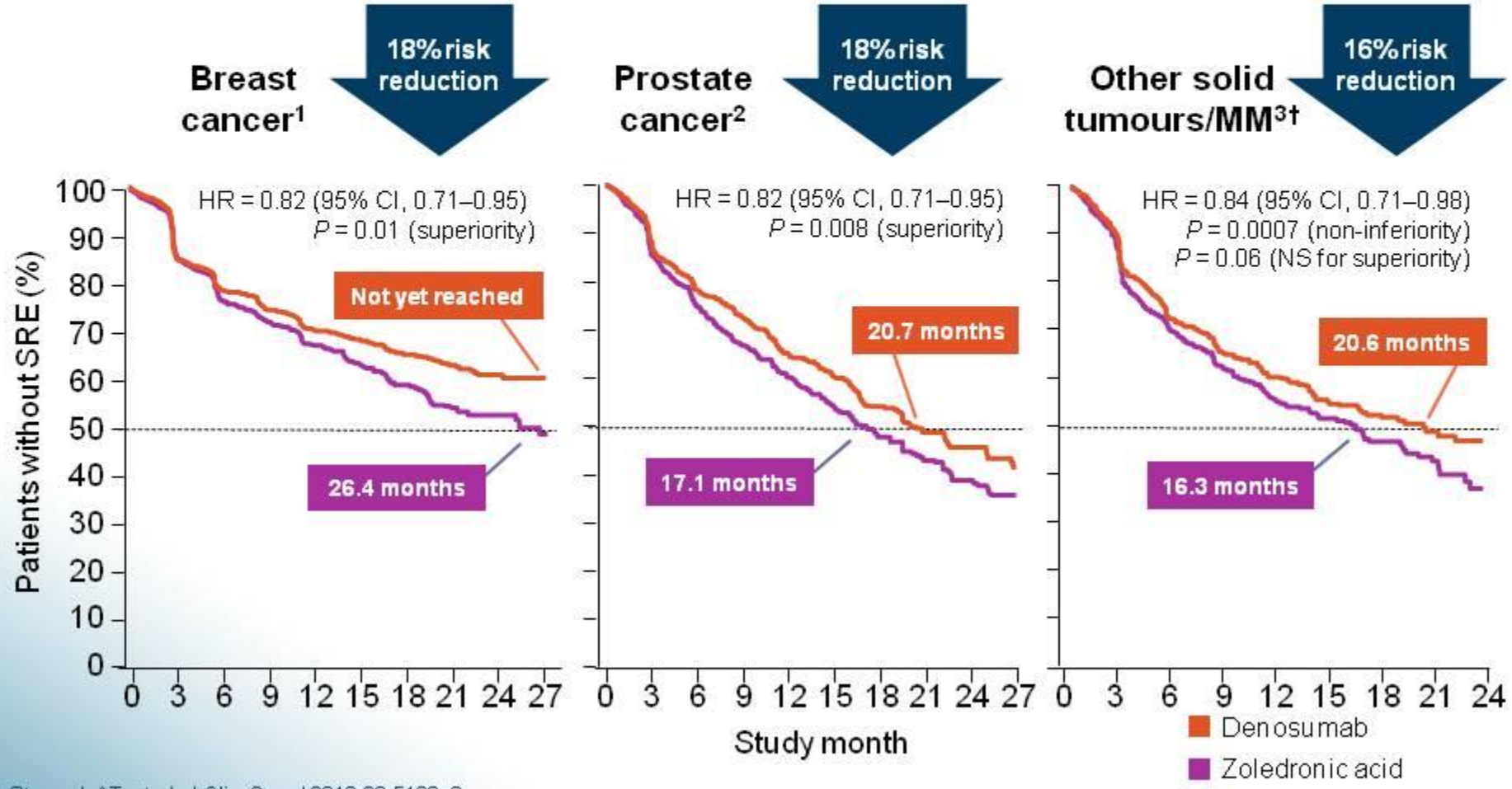

**Time to first SRE**

**17% Risk Reduction**

HR=0.83
(95% CI, 0.76–0.90)
p<0.001 (superiority)

Lipton A, et al. Eur J Cancer 2012;48(16):3082–92.

# Risk reduction in time to first SRE consistently favoured denosumab across tumour types




1. Stopeck AT, et al. J Clin Oncol 2010;28:5132–9;
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3. Henry DH, et al. J Clin Oncol 2011;29:1125–32.

†Excluding breast and prostate. All data from primary analyses.
MM, multiple myeloma; NS, non-significant.

# Thank you

# Trials of Shorter Durations of Adjuvant Trastuzumab

| Trial | Sample | Recruitment Time | Timing of randomization | Patient characteristics | Chemotherapy | | Prespecified non inferiority margin | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | % A and T | % concomitant trastuzumab | | |
| **6 months vs 12 months** | | | | | | | | |
| PHARE (1) | 3380 | 6 y | at 6 m | N- 55%<br>ER+ 58% | 74% | 56% | 1.15 | DFS events at 2 y<br>8.9% vs 6.2%<br>HR 1.28 (1.05-1.56) |
| HORG (2) | 481 | 8 y | upfront | N- 21%<br>ER+ 67% | 100% | 100% | 1.53 | DFS events at 3 y<br>6.7% vs 4.3%<br>HR 1.57 (0.86-2.10) |
| PERSEPHONE (3) | 4089 | 8 y | within first 6 m | N- 59%<br>ER+ 69% | 48% | 47% | 1.29 | DFS events at 4 y<br>11.6% vs 11.2%<br>HR 1.07 (0.93-1.24) |
| **9 weeks vs 12 months** | | | | | | | | |
| SHORT-HER (4) | 1253 | 9 y | upfront | N- 53%<br>ER+ 68% | 100% | 100% | 1.29 | DFS events at 5 y<br>14.6% vs 12.5%<br>HR= 1.15 (90% CI 0.91-1.46) |
| SOLD (5) | 2176 | 9 y | upfront | N- 60%<br>ER+ 66% | 100% | 100% | 1.3 | DFS events at 5 y<br>12% vs 9.5%<br>HR 1,39 (90% CI 1.12-1.72) |

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# Cardiotoxicity in trials of « shorter durations » of trastuzumab

| | Sample | Timing of randomization | % receiving | | LEVF monitoring | Cardiac events Shorter vs longer trastuzumab |
|---|---|---|---|---|---|---|
| | | | anthracyclines | Concom trastuzumab | | |
| PHARE | 3384 | At 6 months* | 88.8% | 56.2% | q3m for 2y then 6m | 1.9% vs 5.7% |
| HORG | 481 | Before chemotherapy | 100% | | m until end of atment | 0 vs 2 cases |
| PERSEPHONE | 4089 | Any time up to the 9th cycle | | | q3m until end of treatment | 9% vs 12% |
| SHORT-HER | 1253 | | 100% | 100% | Q3m until end of treatment then at 18m | 5.1% vs 14.4% |
| SOLD | 2176 | Before chemotherapy | 100% | 100% | At w18, 31, 43, 61 and 36m | 2.0 vs 3.9% |

**Less « cardiotoxicity » with shorter trastuzumab duration in all trials !**

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