



## What to do after pCR in different subtypes?

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**Policlinico di Modena, Italy**

**Modena Cancer Center**

## Aims of neoadjuvant therapy in breast cancer

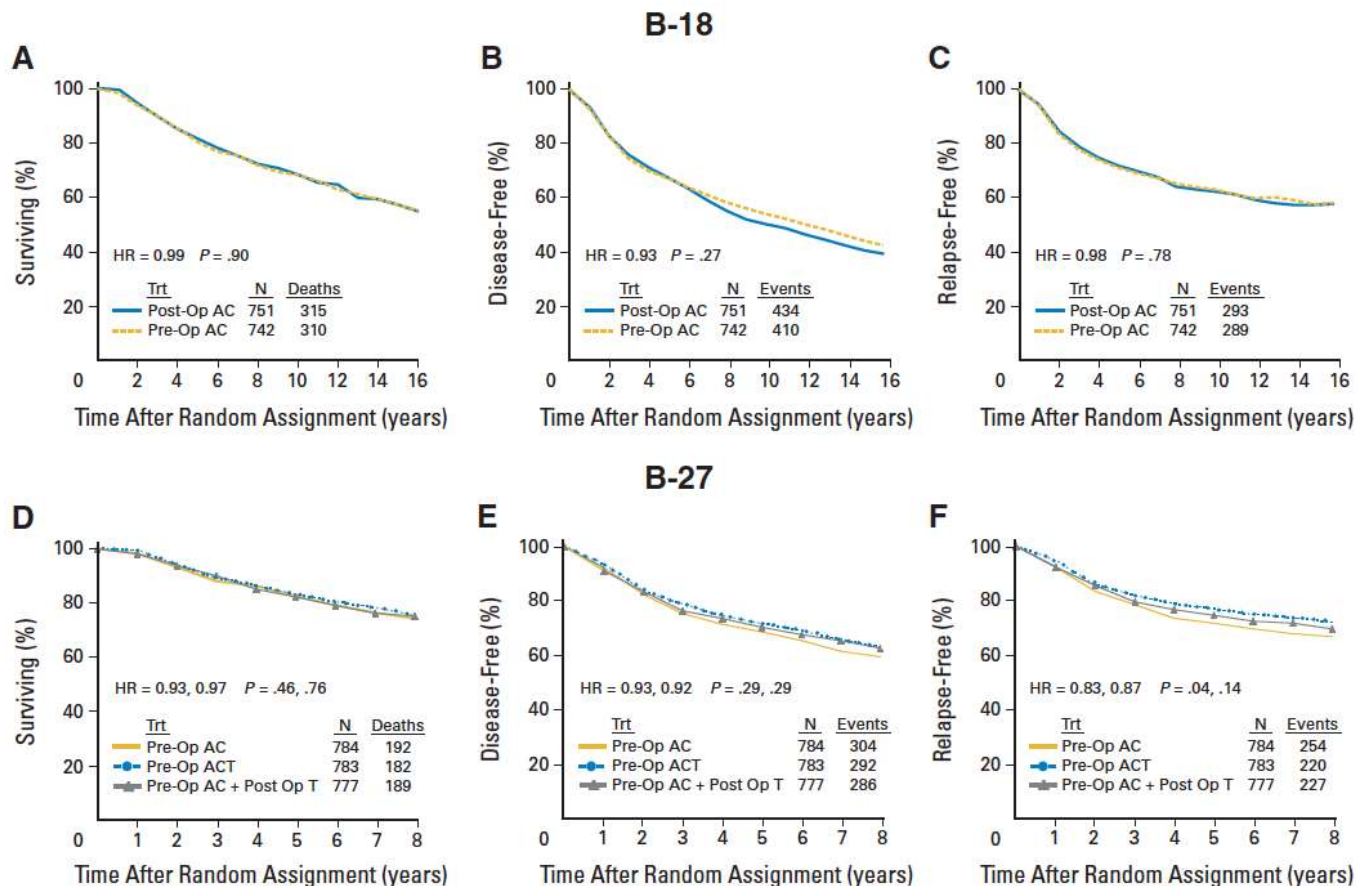
	Primary	Secondary	
<b>Locally advanced breast cancer</b>	To improve surgical options	To obtain freedom from disease	To gain information on tumor response
<b>Operable breast cancer and candidates for <b>adjuvant chemotherapy</b></b>	To improve surgical options	To obtain freedom from disease	To gain information on tumor response
<b>Operable breast cancer and candidates for <b>adjuvant endocrine treatment alone</b></b>	To improve surgical options	to gain information on tumor response	

## Neoadjuvant chemotherapy allowed to:

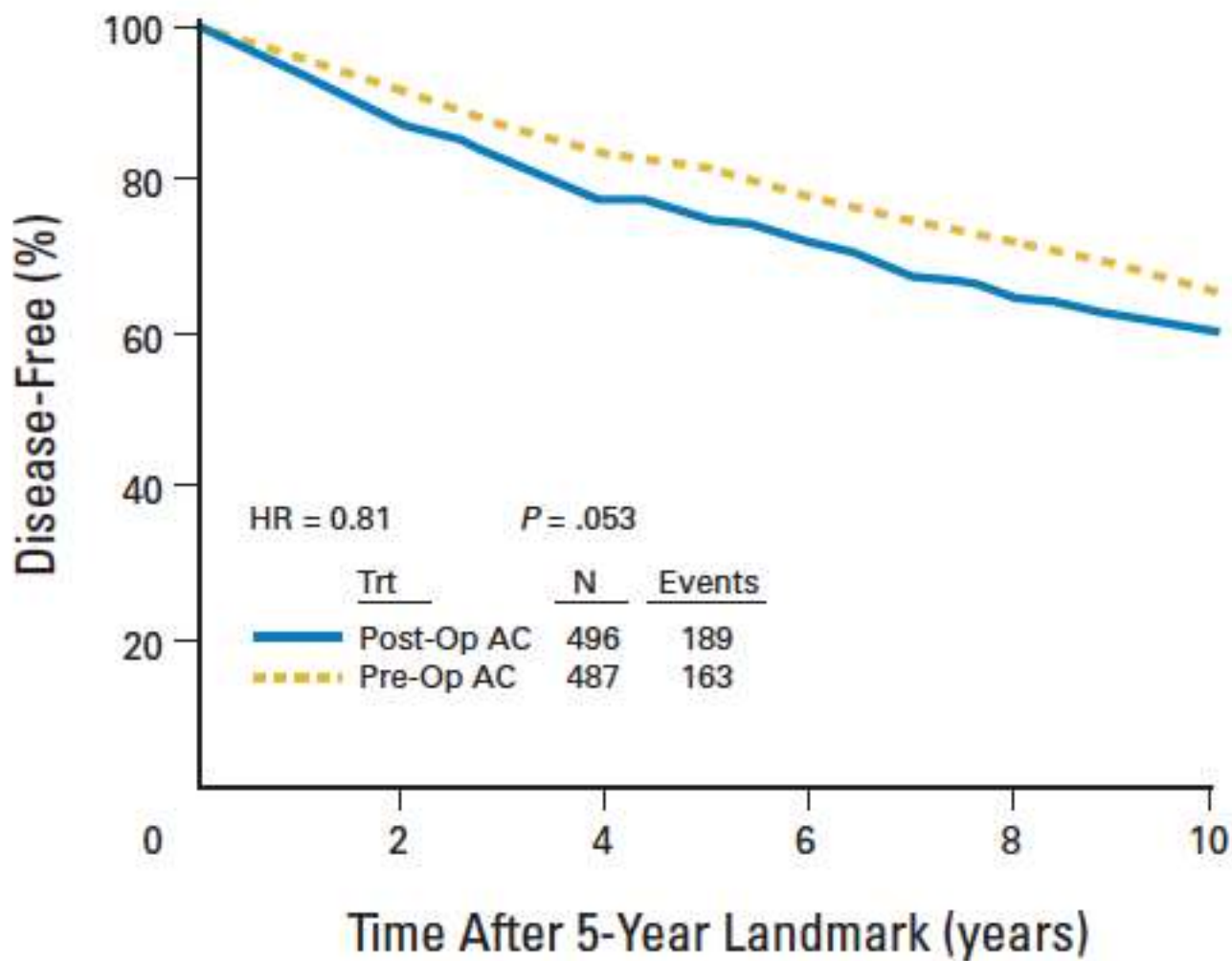
Administer the chemotherapy plan before surgery

- Opportunity to observe in vivo tumor sensitivity
- Evaluate to de-escalate treatment in some subtypes
- Increase the rate of Breast Conservative Surgery
- Avoid adjuvant chemotherapy

# Preoperative Chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27



Rastogi P J Clin Oncol 26:778-785. © 2008



Rastogi P J Clin Oncol 26:778-785. © 2008

## Neoadjuvant chemotherapy leads to (1)

Increased use of the rate of breast-conserving surgery (BCS)

- The rate of BCS is higher in patients who have a cCR or cPR.
- The rate of BCS is higher in patients who have been treated at a center with experience administering such treatments.

## Neoadjuvant chemotherapy leads to (2)

Increased rate of pathological response

- The pathological complete response pCR is a surrogate of survival benefit (EFS and OS)
- DFS and OS are equivalent in patients treated with the same adjuvant or neoadjuvant regimen.



# Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer

Tatiana M. Prowell, M.D., and Richard Pazdur, M.D.

## Guidance for Industry

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

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

October 2014

*“We believe that use of pCR as an endpoint to support accelerated approval in the neoadjuvant setting has the potential to help address unmet need in **high-risk populations** in a far shorter time frame than would be required via the conventional approach to breast cancer drug development”*

N ENGL J MED 366;26 NEJM.ORG JUNE 28, 2012

## Which definition of pathological complete response – pCR ?

ypT0 ypN0

(ie, absence of invasive cancer and in-situ cancer in the breast and axillary nodes),

ypT0/is ypN0

(ie, absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ),

ypT0/is

(ie, absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement).

## Which definition of pathological complete response – pCR ?

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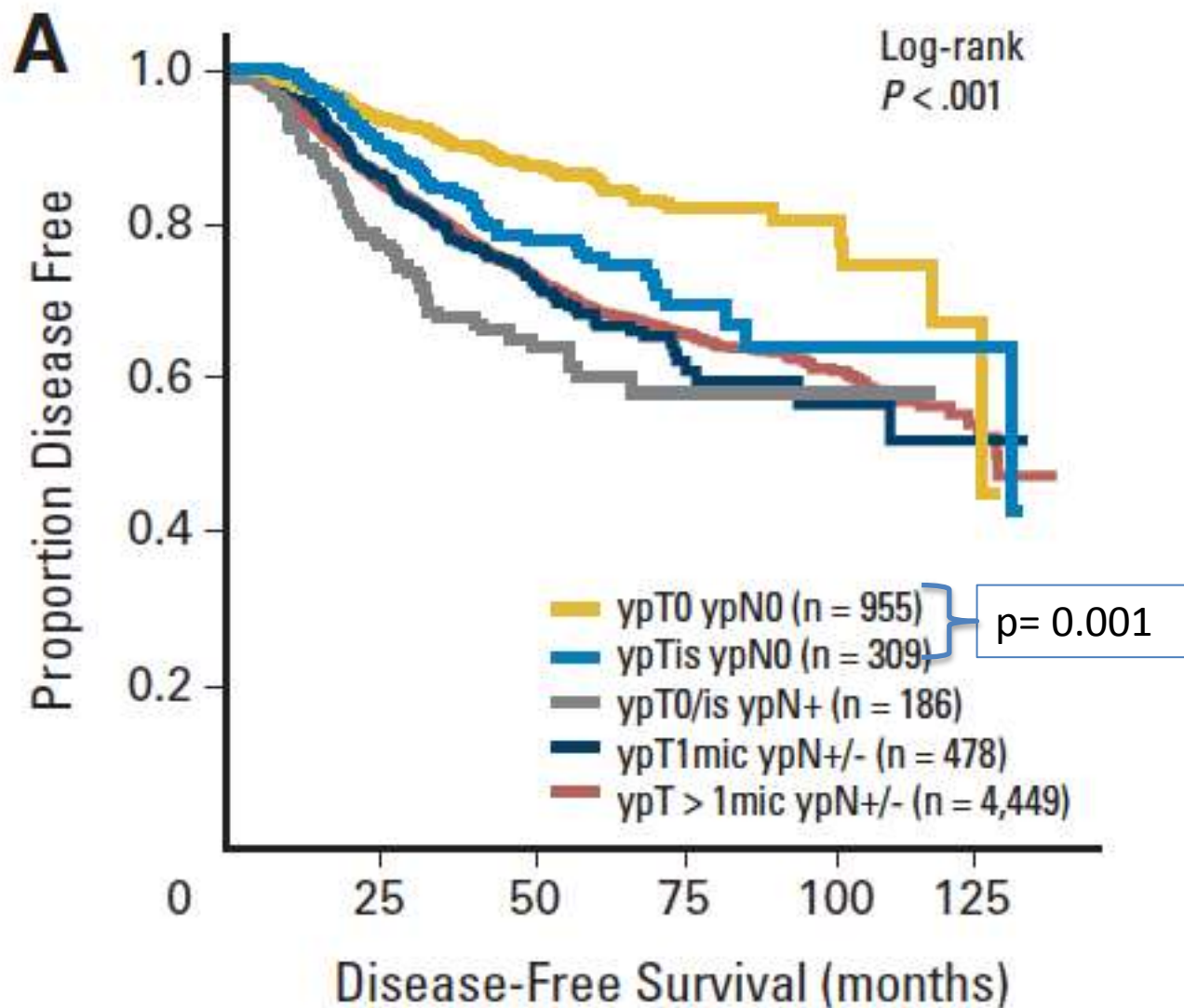
ypT0/is ypN0

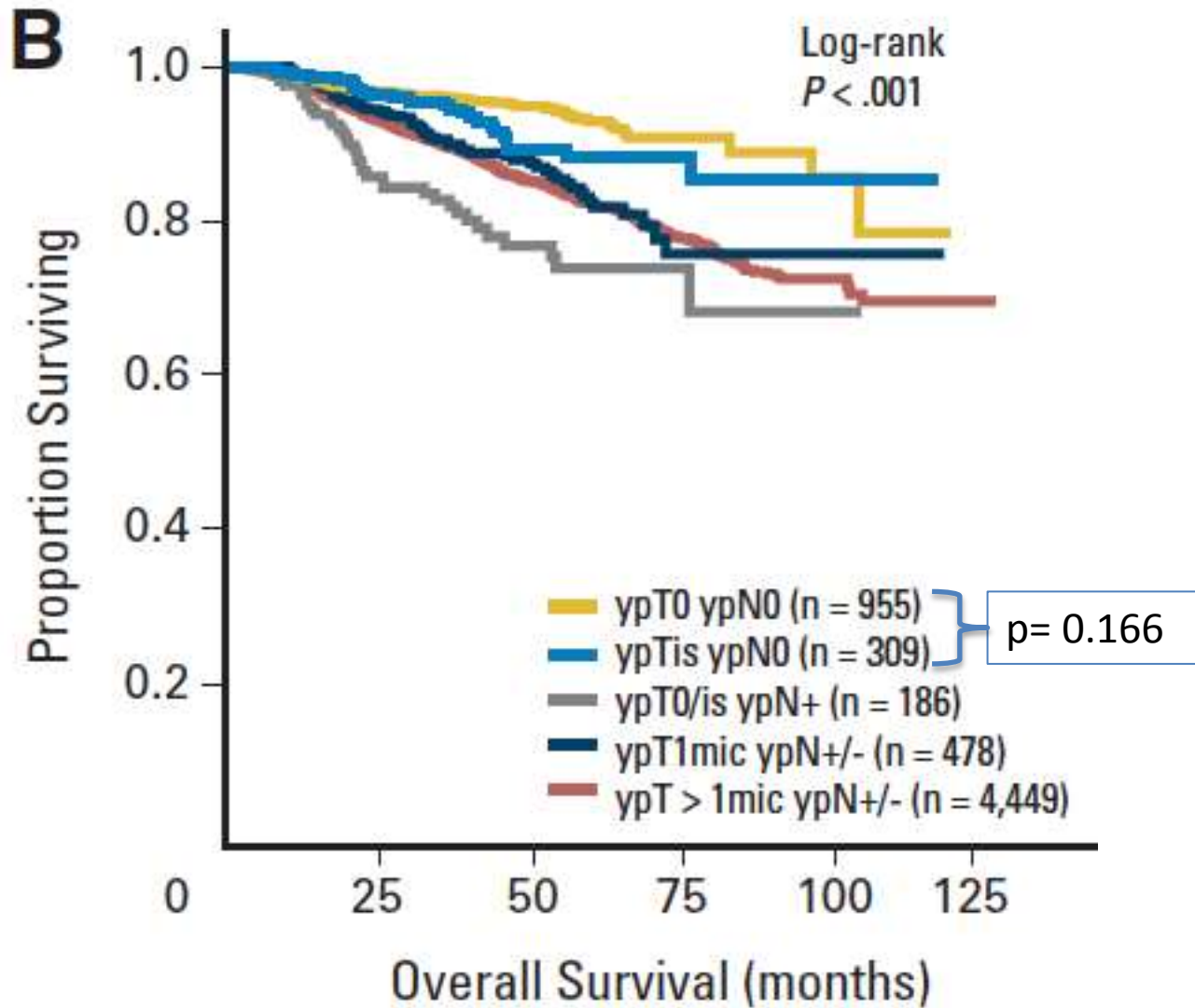
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ypT0/is

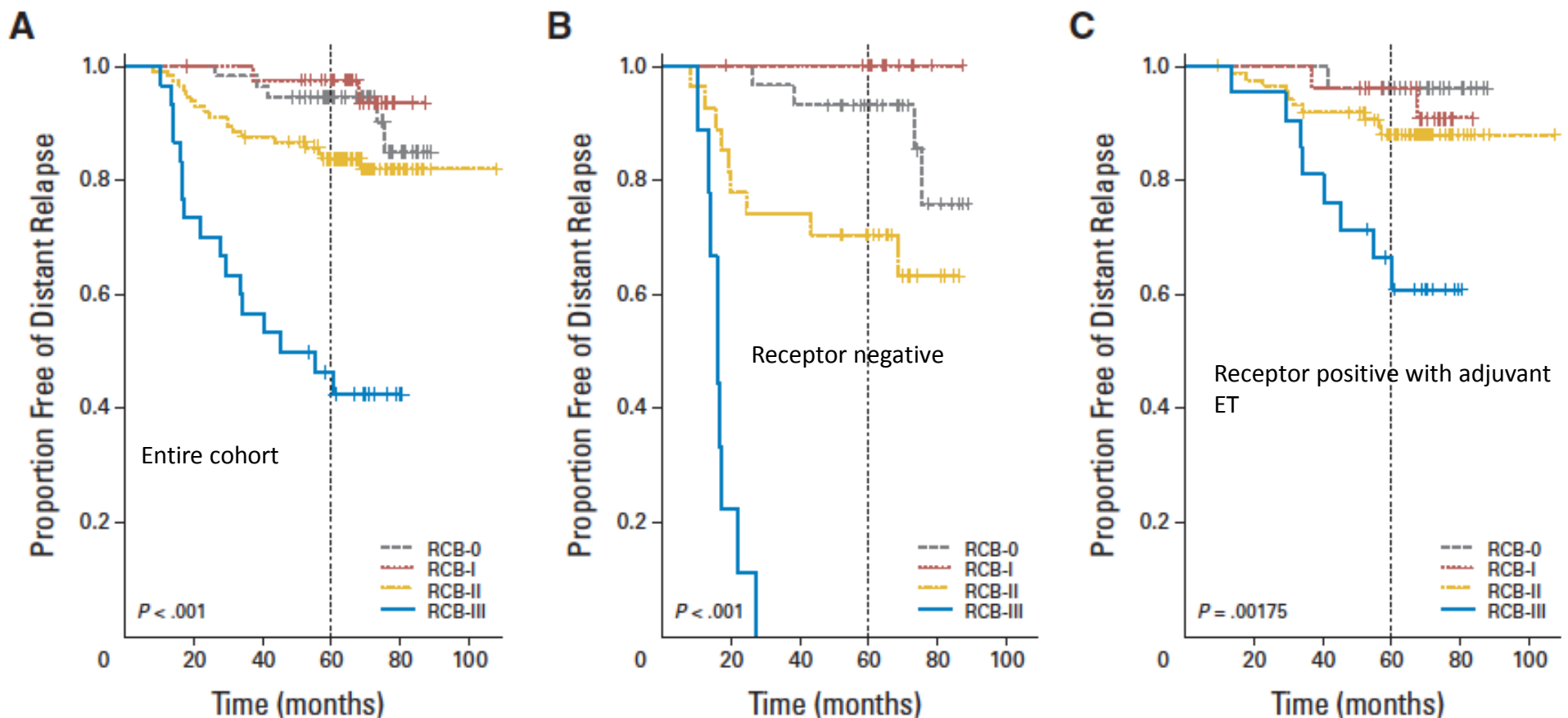
(ie, absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement).

*von Minckwitz G J Clin Oncol. 2012 May 20;30(15):1796-804*





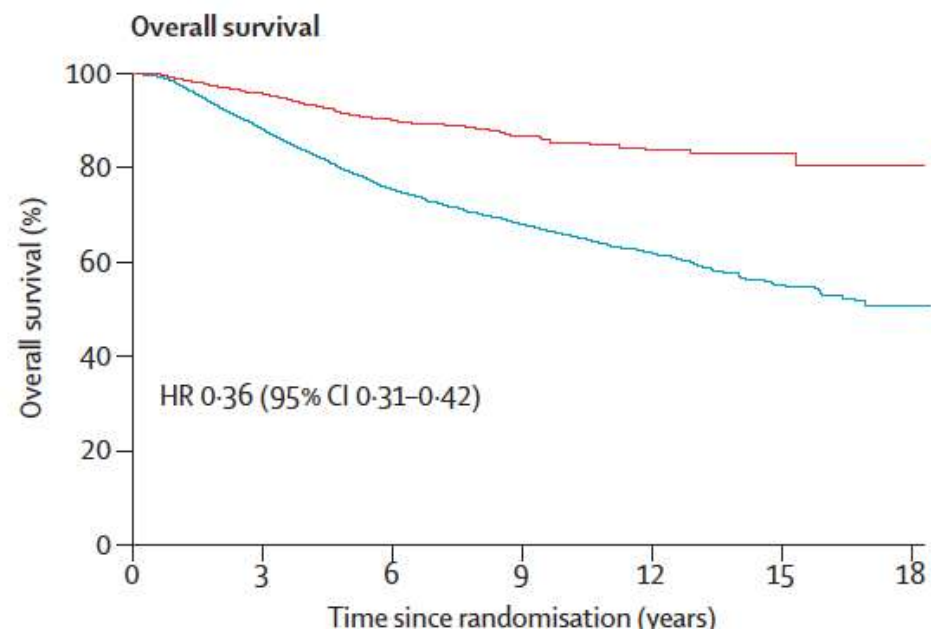
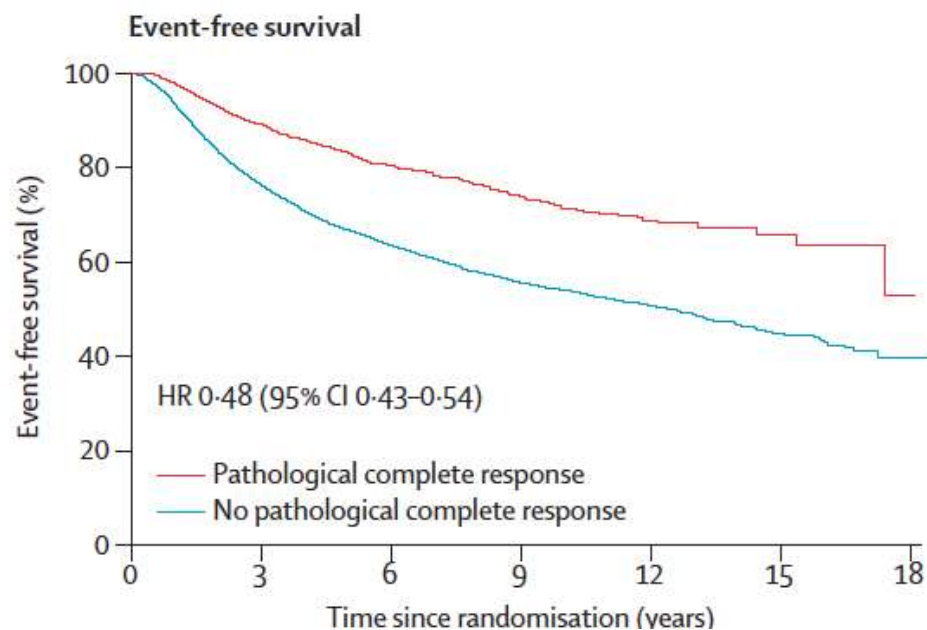
# Impact of Residual Cancer Burden after Neoadjuvant chemotherapy



*Residual cancer burden (RCB) was calculated as a continuous index combining pathologic measurements of primary tumor (size and cellularity) and nodal metastases (number and size) for prediction of distant relapse-free survival (DRFS) in multivariate Cox regression analyses.*

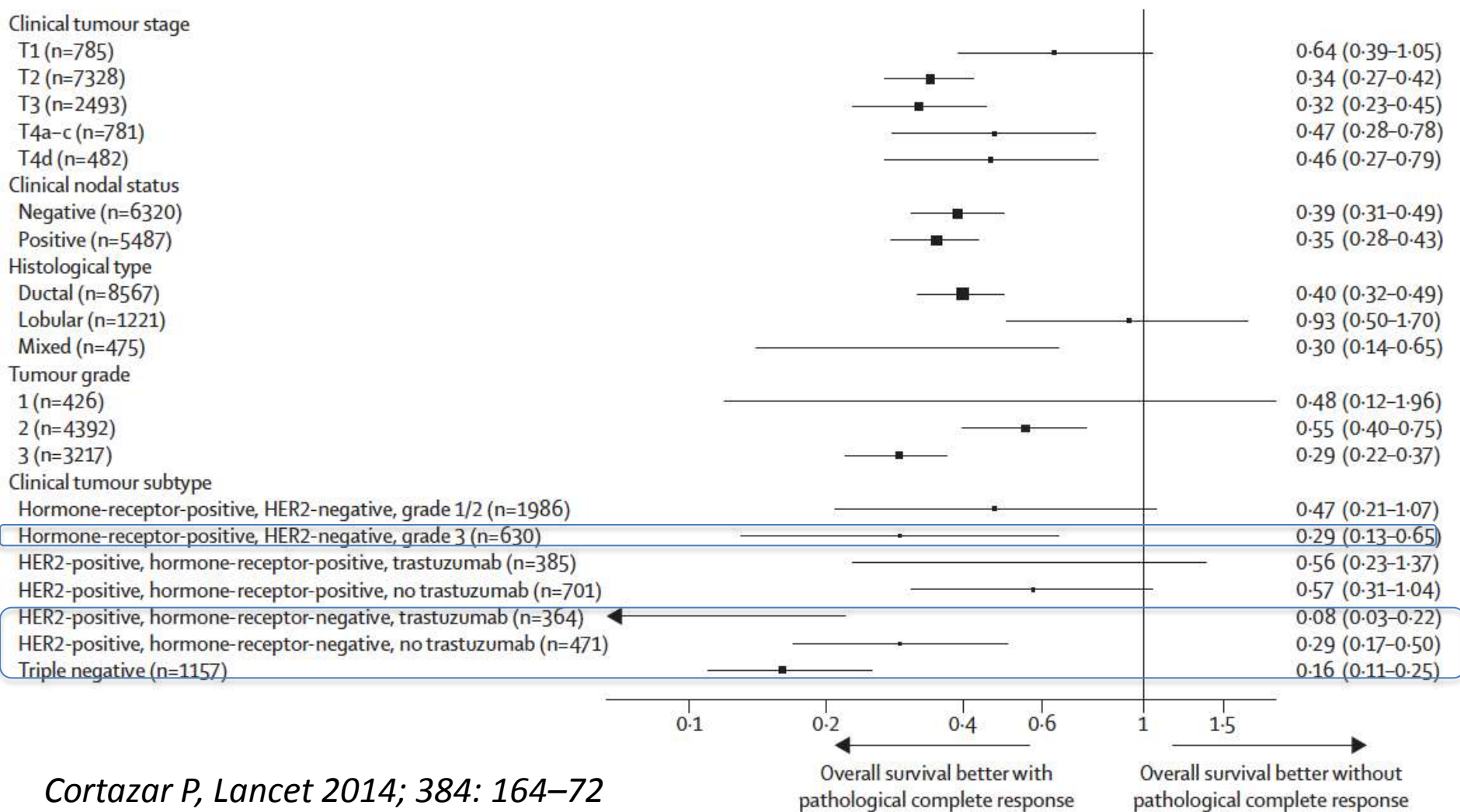
*Symmans VF J Clin Oncol. 2007 Oct 1;25(28):4414-22*

## Residual disease in the breast had a prognostic relevance



*Cortazar P, Lancet 2014; 384: 164–72*

# Residual disease in the breast had a prognostic relevance



Cortazar P, Lancet 2014; 384: 164-72

**pCR could be a suitable intermediate endpoint  
for patients with TN, high-grade HR-positive,  
and HER2-positive  
breast tumors  
*but not for low-grade HR-positive tumors.***

San Antonio Breast Cancer Symposium®, December 4-8, 2018

# **Pathological complete response (pCR) after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival, stratified by breast cancer subtypes and adjuvant chemotherapy usage: Patient-level meta-analyses of over 27,000 patients.**

Laura M. Spring MD<sup>1,3</sup>; Geoffrey Fell MS<sup>2</sup>; Andrea Arfe MS<sup>5</sup>; Rachel Greenup MD, MPH<sup>6</sup>; Kerry L. Reynolds MD<sup>1,3</sup>; Barbara L. Smith MD, PhD<sup>1,3</sup>; Beverly Moy MD, MPH<sup>1,3</sup>; Steven J. Isakoff MD, PhD<sup>1,3</sup>; Lorenzo Trippa PhD<sup>2,4</sup>; Giovanni Parmigiani PhD<sup>2,4</sup>; Aditya Bardia MD, MPH<sup>1,3</sup>

1. Massachusetts General Hospital Cancer Center, Boston, MA
2. Dana-Farber Cancer Institute, Boston, MA
3. Harvard Medical School, Boston, MA
4. Harvard TH Chan School of Public Health, Boston, MA
5. Bocconi University, Milan, Italy
6. Duke University, Durham, NC

# Study Objectives

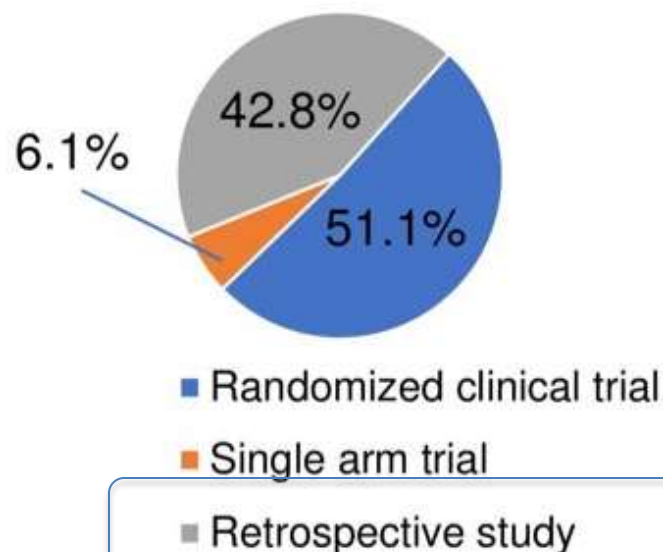
To conduct a comprehensive meta-analysis of studies on neoadjuvant chemotherapy for localized breast cancer using recapitulated patient level data to evaluate:

- association between pCR and clinical outcomes (EFS and OS) by breast cancer subtype,
- impact of adjuvant chemotherapy on association between pCR and clinical outcomes,
- magnitude of change in pCR ( $\Delta$  pCR) and corresponding change in clinical outcomes ( $\Delta$  EFS)

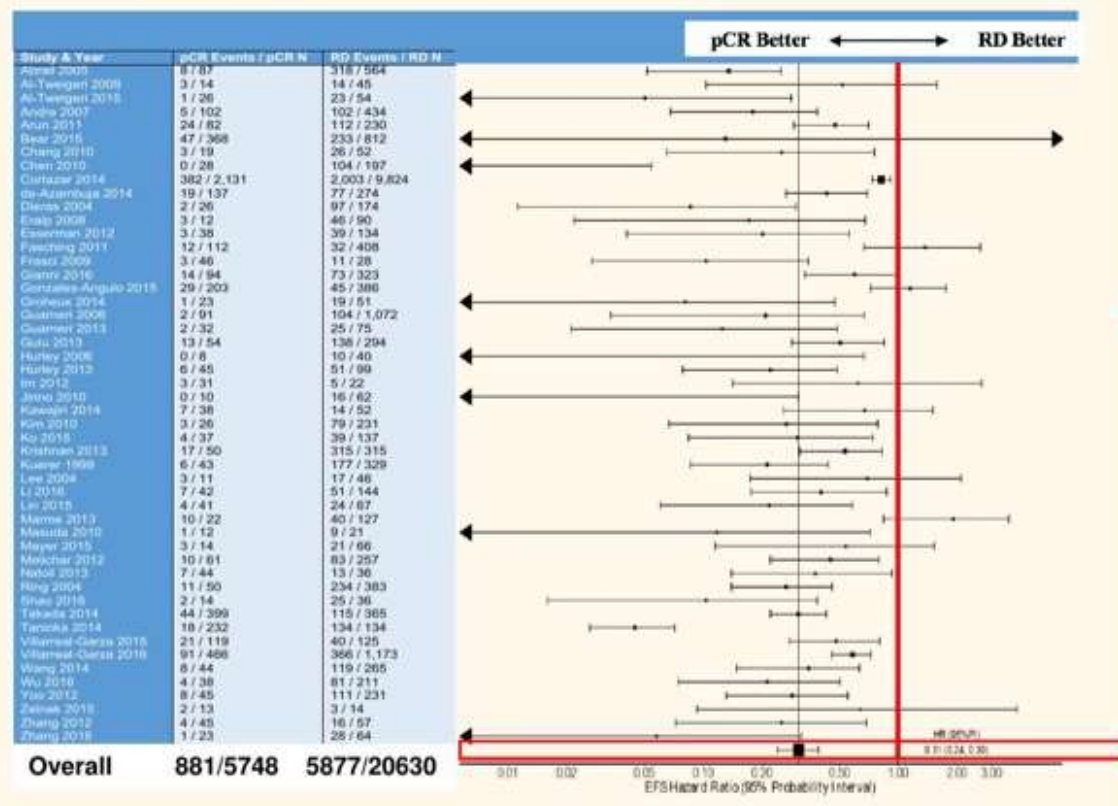
# Results: Select Study Characteristics

- Publication dates (range): 1999-2016
- Broad global patient population, including United States, Mexico, Europe, Kuwait, Saudi Arabia, China, Japan, and Korea
- Median follow-up for recurrence (range): 48 months (21.3-107)
- Median follow-up for survival (range): 49.9 months (31.2-118)

% Patients by Type of Study

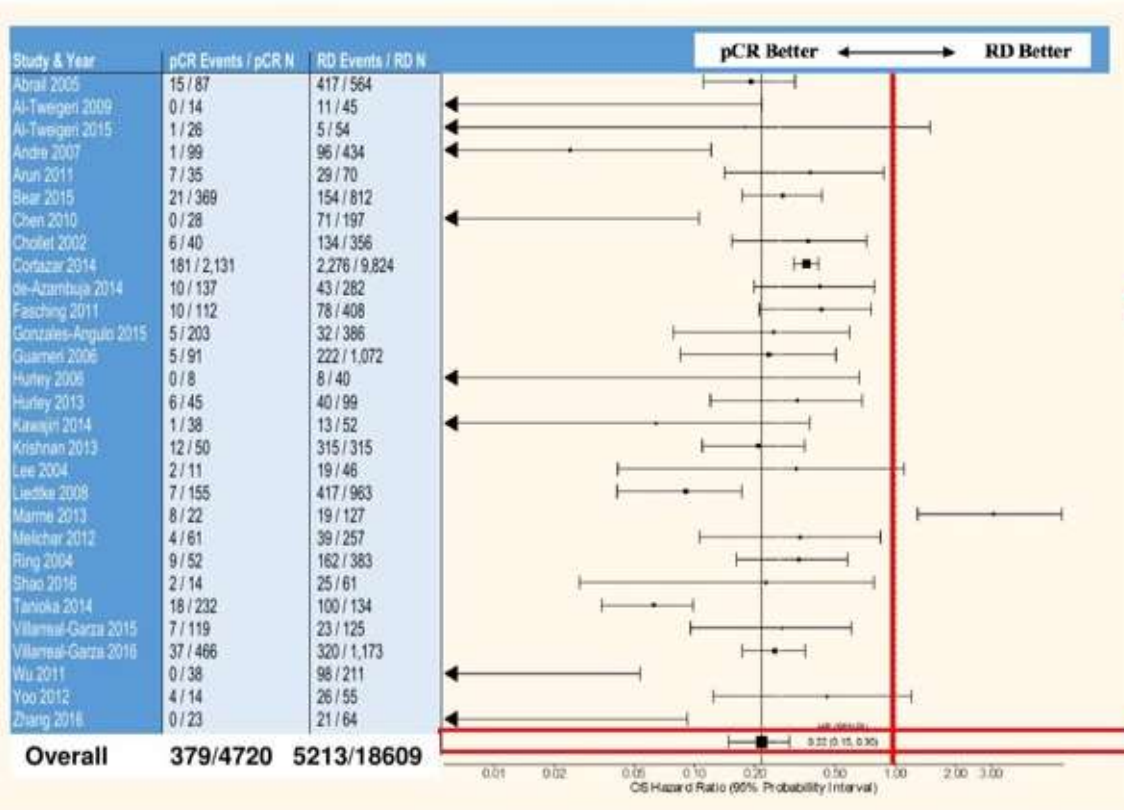


# Results: pCR and EFS



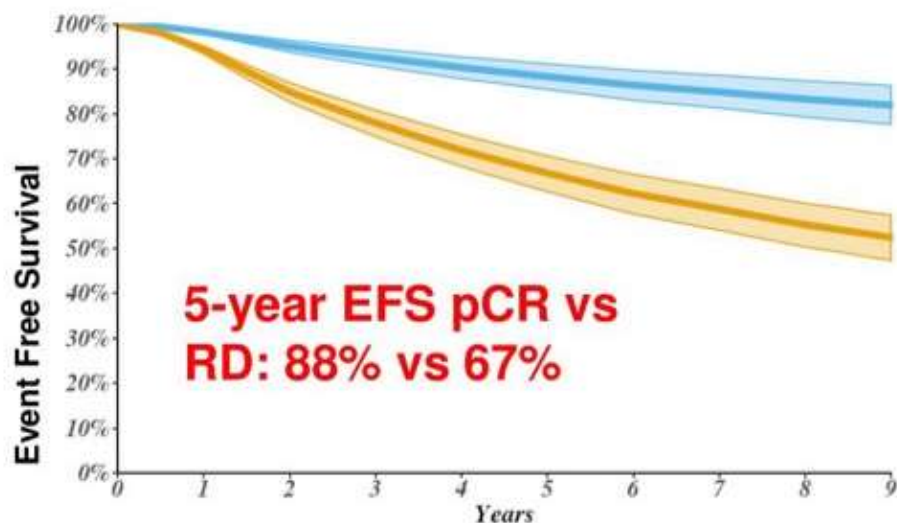
Patients who had pCR, compared to those with residual disease (RD), had significantly better **EFS** (HR 0.31, 95% PI: 0.24-0.39, N = 26,378).

# Results: pCR and OS

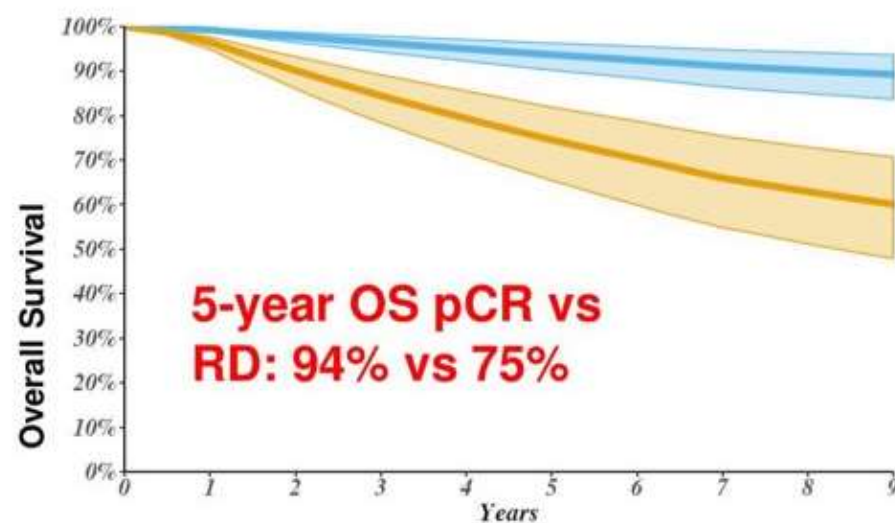


Patients who had pCR, compared to those with residual disease (RD), had significantly better **OS** (HR 0.22, 95% PI: 0.15-0.30, N = 23,329).

# Results: EFS and OS in Overall Population



**5-year EFS pCR vs  
RD: 88% vs 67%**



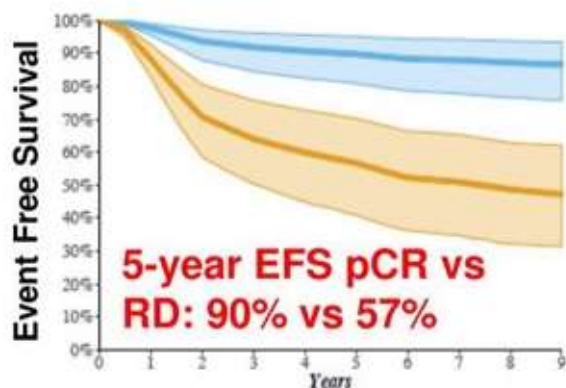
**5-year OS pCR vs  
RD: 94% vs 75%**

**Blue:** pCR group

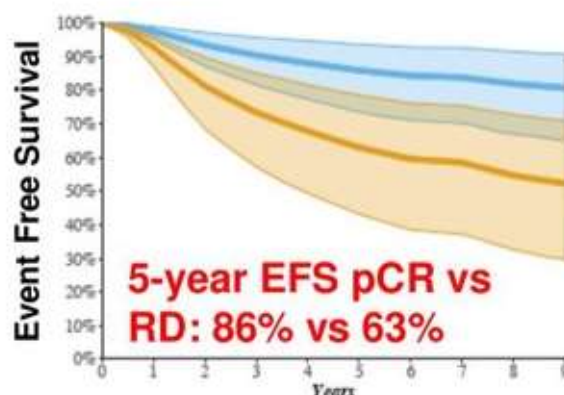
**Orange:** Residual disease (RD) group

# Results: EFS and OS by Subtype

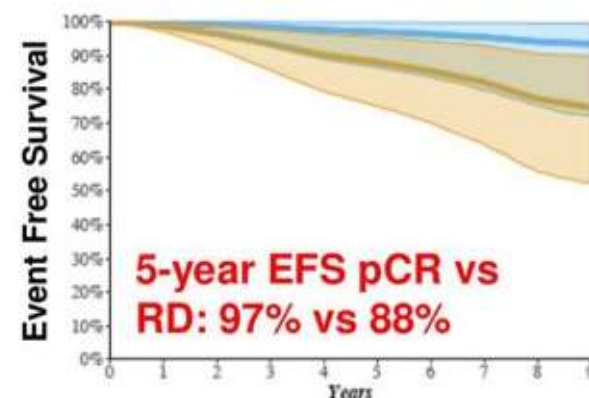
TNBC



HER2+



HR+/HER2-

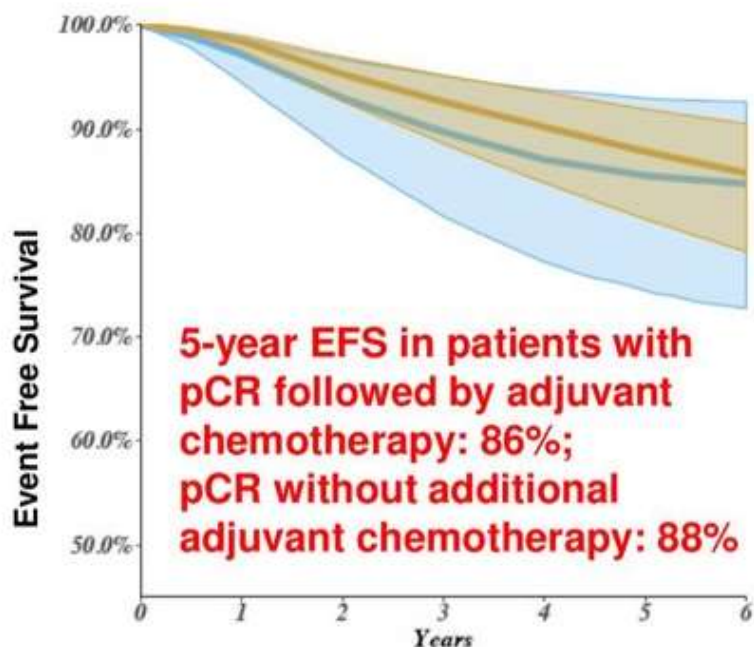


**Blue:** pCR group

**Orange:** Residual disease (RD) group

**Similar results seen with OS**

# Results: Adjuvant Chemotherapy



**Blue:** pCR without adjuvant chemotherapy  
**Orange:** pCR with adjuvant chemotherapy

Adjuvant Chemotherapy	Hazard Ratio (pCR and EFS)	95% PI
Yes <sup>1</sup>	0.36	0.19-0.67
No <sup>2</sup>	0.36	0.27-0.54

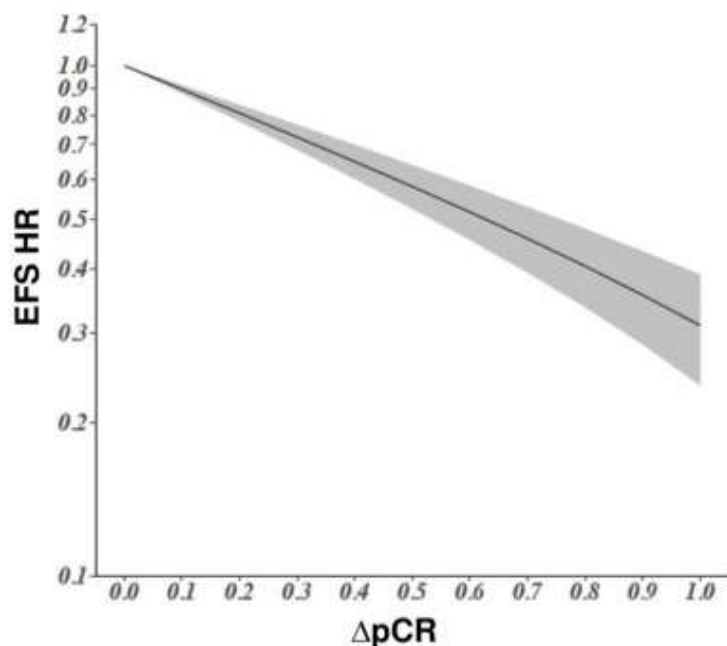
pCR was associated with significantly improved EFS in both groups, and there was no significant difference in Hazard Ratios between the two groups<sup>3</sup>.

<sup>1</sup> >90% of patients received adjuvant chemotherapy

<sup>2</sup> No more than 10% of patients received adjuvant chemotherapy

<sup>3</sup> Paired T-test (difference in log-HR: 0.02, 95% PI: -0.75-0.73; p = 0.60)

# Results: $\Delta$ EFS vs. $\Delta$ pCR



Change in ( $\Delta$ ) pCR*	Corresponding HR (EFS)	95% PI
0	1	N/A
0.1	0.90	0.88-0.92
0.2	0.81	0.78-0.84
0.3	0.72	0.68-0.77
0.4	0.65	0.60-0.70
0.5	0.58	0.52-0.64
0.6	0.52	0.46-0.58
0.7	0.46	0.39-0.53
0.8	0.40	0.34-0.48
0.9	0.36	0.28-0.43
1	0.31	0.24-0.39

Assuming pCR is a valid surrogate endpoint (i.e. it mediates all treatment effects) and average\* pCR of 50%, the magnitude of pCR change is predictive of treatment effects on EFS within a certain amount of uncertainty, based on the model.

## $\Delta$ EFS vs. $\Delta$ pCR (Example)

- For example, the CALGB 40603 trial resulted in **pCR improvement of 13%** (41%  $\rightarrow$  54%) with the addition of carboplatin to standard chemotherapy, which would correspond to an **EFS HR  $\sim$  0.87 (95% PI: 0.84-0.89)**, based on our prediction model.
- Assuming 80% power and a 1:1 randomization ratio, **1,381 events must be observed** to achieve statistical significance at 0.05 level (two-sided).
- In CALGB 40603 the HR for EFS for carboplatin was 0.84 (95% confidence interval: 0.58-1.22), but this was not statistically significant (**only 110 events were observed during follow-up**).
- Common theme for neoadjuvant studies, which are typically powered for primary endpoint of pCR and not secondary long-term survival outcomes.

# Strengths and Limitations

- Strengths of the study include:
  - large sample size
  - inclusion of both trial and retrospective studies
  - Inclusion of patients across the globe
  - results highly significant despite inclusion of a variety of neoadjuvant regimens, suggesting the path taken to attain a pCR may not be critical
- Limitations of the study include:
  - variability in study population and regimens received
  - variability in study specific outcome definitions
  - variability in the definition of hormone-receptor positivity
  - inability to assess other surrogate endpoints such as the residual cancer burden index

# Conclusions

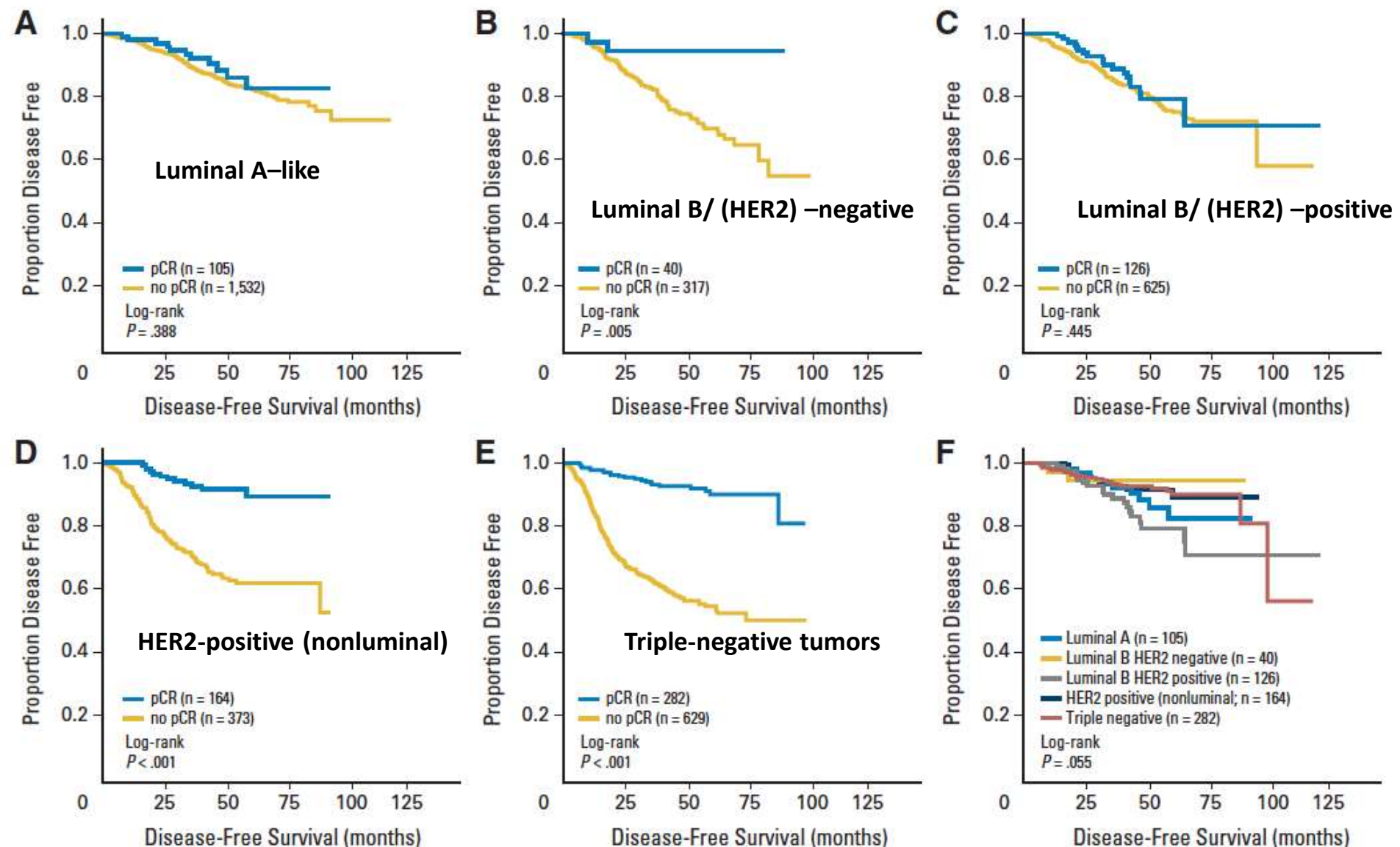
- **Achieving pCR following neoadjuvant chemotherapy is associated with significantly improved EFS and overall survival, particularly for triple negative and HER2+ breast cancer.**
- **The similar outcomes with or without adjuvant chemotherapy in patients who attain pCR after neoadjuvant chemotherapy likely reflects tumor biology and suggests adjuvant chemotherapy could potentially be omitted in certain circumstances.**
- **Further research is needed to evaluate the clinical utility of escalation/de-escalation strategies in the adjuvant setting based on neoadjuvant response.**

## But what about pCR in the different subtypes?

The results by Spring et al

- Confirm the prognostic significance of pCR
- Especially in the TNBC and Her2-positive subtypes

# The importance of being pCR in various subtypes

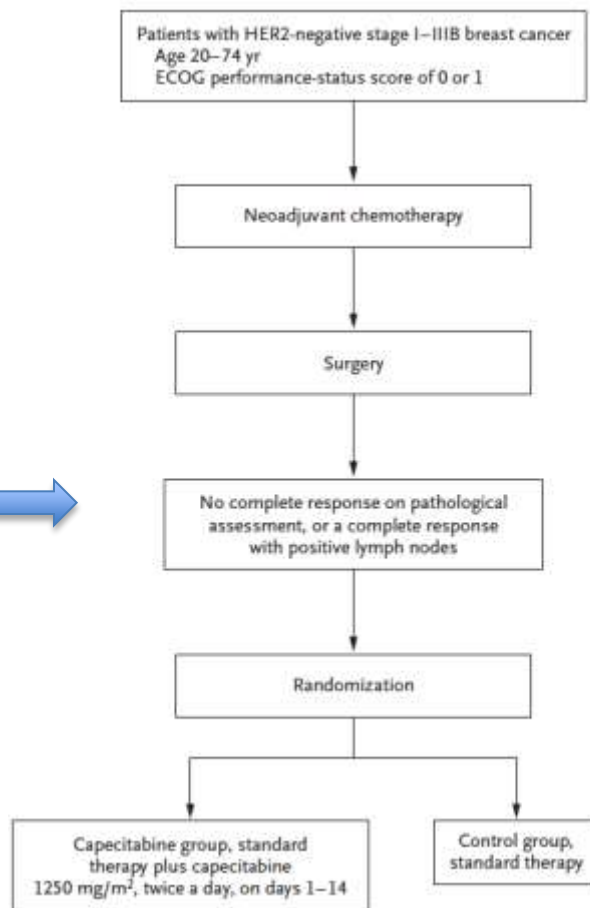
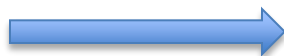


von Minckwitz G J Clin Oncol. 2012 May 20;30(15):1796-804

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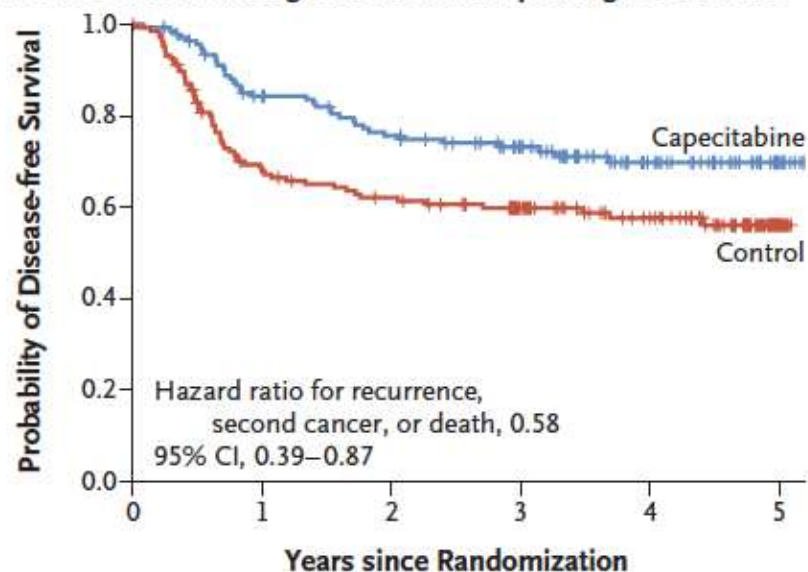
# TNBC

CREATE trial



## CREATE trial

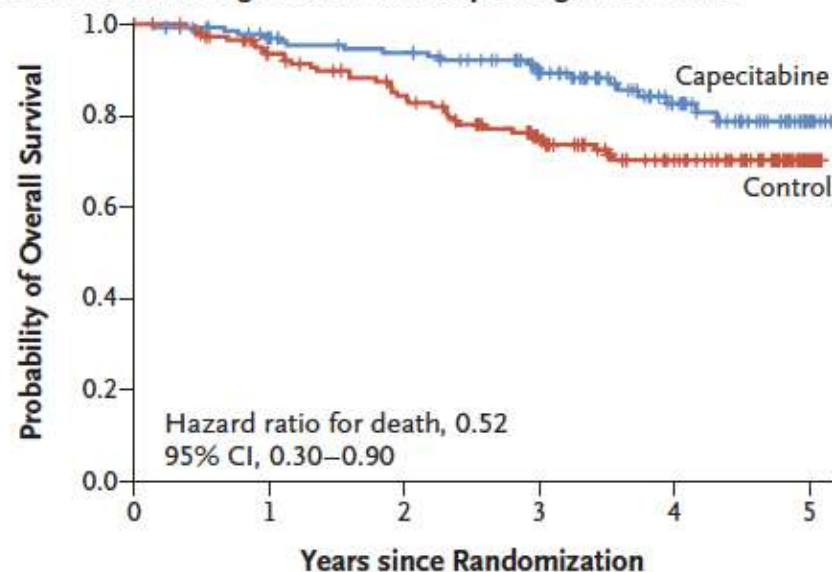
**C Disease-free Survival among Patients with Triple-Negative Disease**



**No. at Risk**

Capecitabine	139	109	96	76	42	11
Control	147	95	84	69	47	6

**D Overall Survival among Patients with Triple-Negative Disease**



**No. at Risk**

Capecitabine	139	124	116	91	50	11
Control	147	125	108	82	52	9

## Study Design

- TNBC: ER-, PR-, HER2- (centrally confirmed)
- T1c-T3, N0-N3a\*, M0
- Prior standard neo/adjuvant CT with anthras +/- taxanes
- Surgery with free-margins

\*except infraclavicular lymph node involvement.

### Stratification Factors:

- Institution
- Basal Phenotype according to CK 5/6 and/or EGFR staining (yes vs no)
- ALN (0 vs 1-3 vs  $\geq 4$ )
- Prior CT (anthras vs anthras + taxanes)

1:1 Randomization

Capecitabine 1000 mg/m<sup>2</sup> p.o.,  
b.i.d. x 14 days every 3 weeks  
x 8 cycles

Observation

Radiation therapy according to institution standards

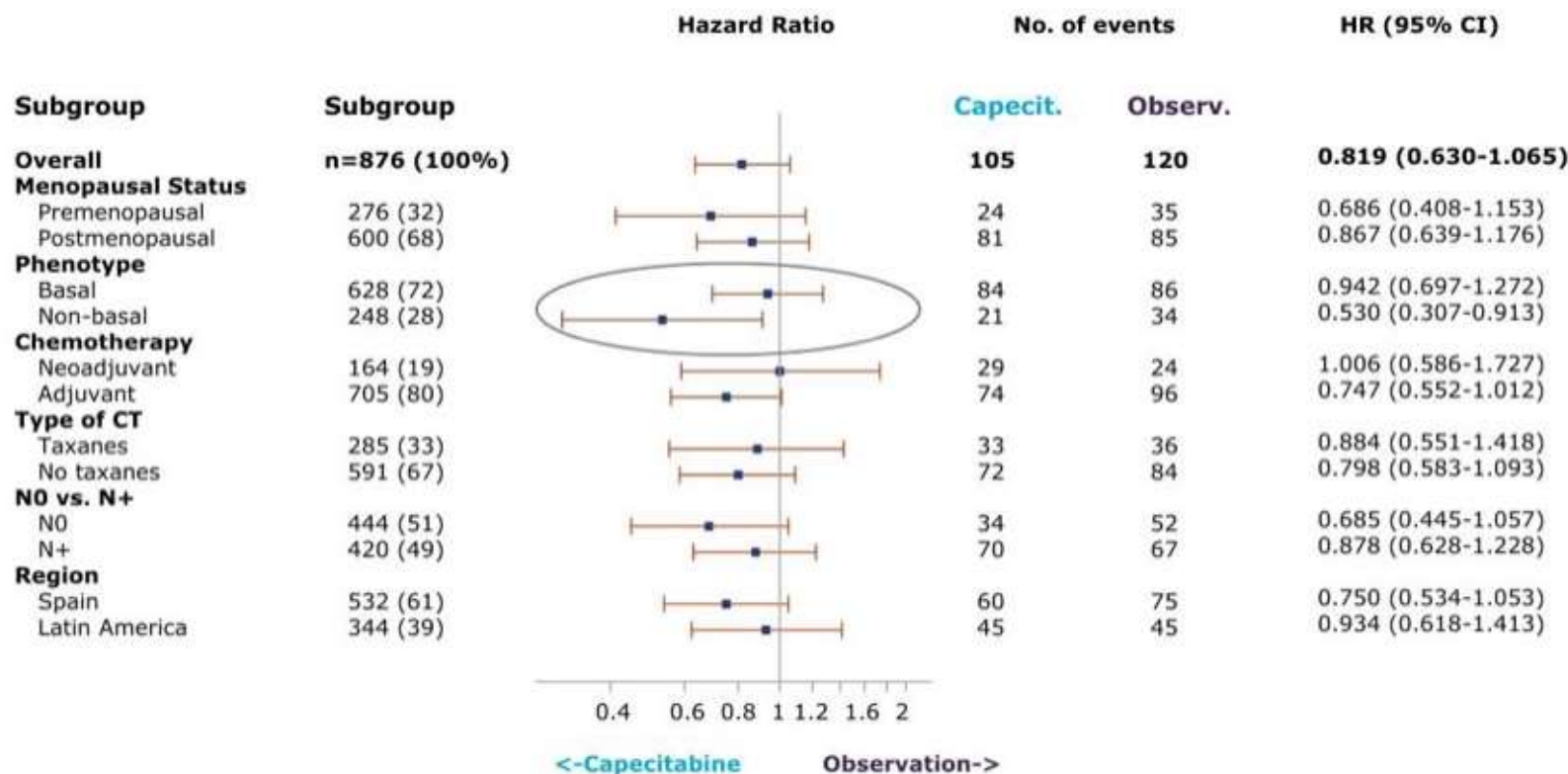
- 6 cy. of standard CT mandatory except for N0 tumors (4 cy. of AC admitted).
- Primary endpoint: Disease-Free Survival (DFS).
- Secondary endpoints: Overall Survival (OS), subgroup analyses, safety, biomarkers.

Abbreviations: ER: Estrogen Receptor. PR: Progesterone Receptor. HER2: Epidermal Growth Factor Receptor 2. CT: Chemotherapy. Anthras: Anthracyclines. CK: Cytokeratins. EGFR: Epidermal Growth Factor Receptor. ALN: Axillary Lymph Nodes. Cy.: Cycles. AC: Doxorubicin + Cyclophosphamide.

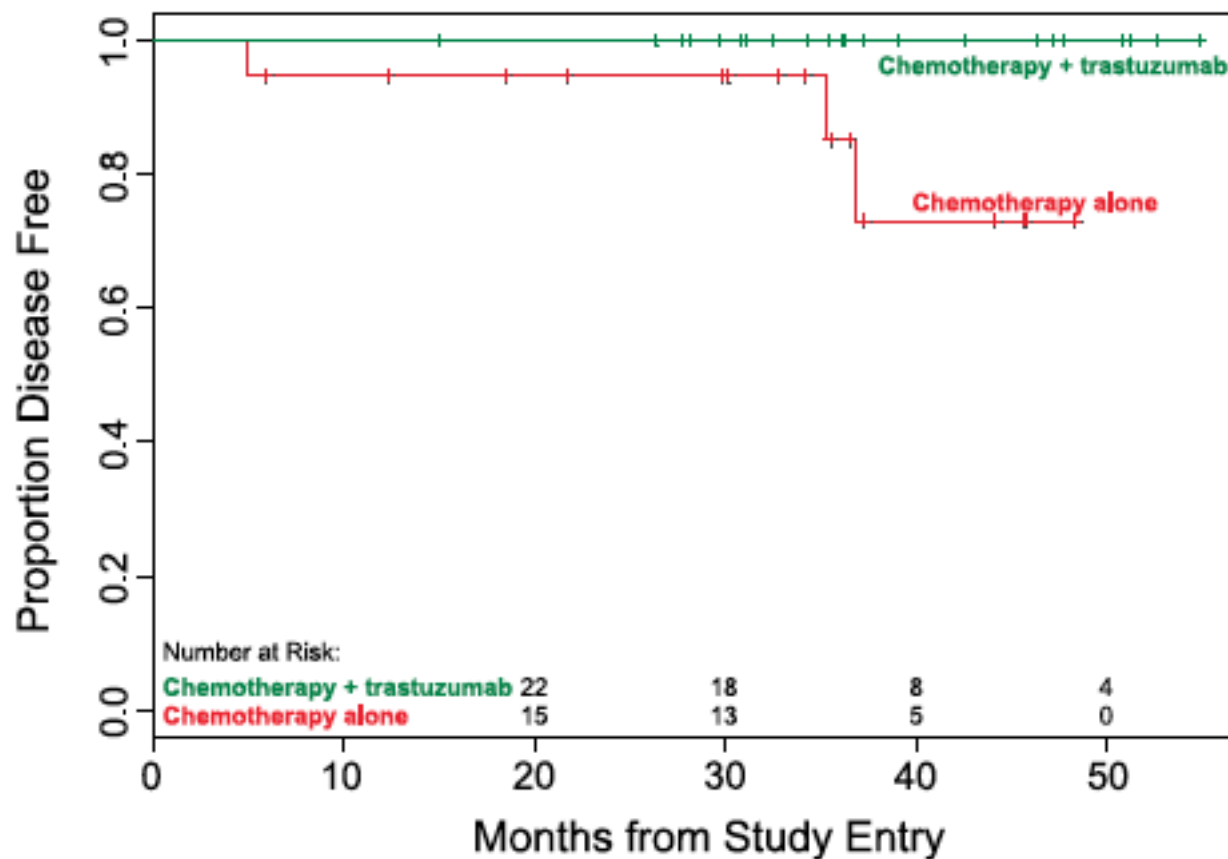
	Capecitabine (n=448)	Observation (n=428)
<b>Type of CT, n (%)</b>		
• Adjuvant (only)	353 (78.8)	352 (82.2)
• Neoadjuvant (+/- adjuvant)	89 (19.9)	75 (17.5)
• Missing data	6 (1.3)	1 (0.2)
<b>pCR in patients with neoadjuvant CT*, n (%)</b>	22 (24.7)	19 (25.3)
<b>CT regimens, n (%)</b>		
• Anthracyclines-based	147 (32.8)	138 (32.2)
• Anthracyclines and Taxanes-based	301 (67.2)	290 (67.8)

\*Pathological complete response in breast and axilla after neoadjuvant chemotherapy.

# Subgroup Analysis of DFS (ITT)



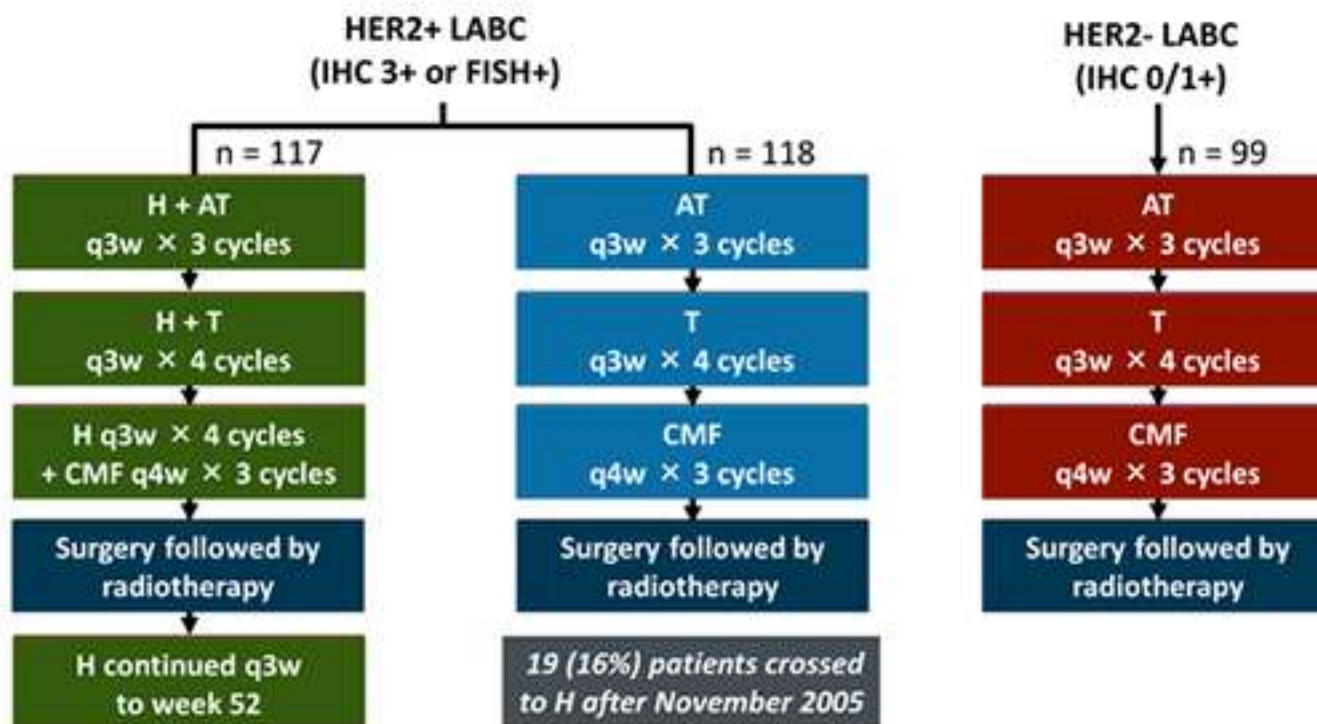
## Her 2+: NACT +/- trastuzumab



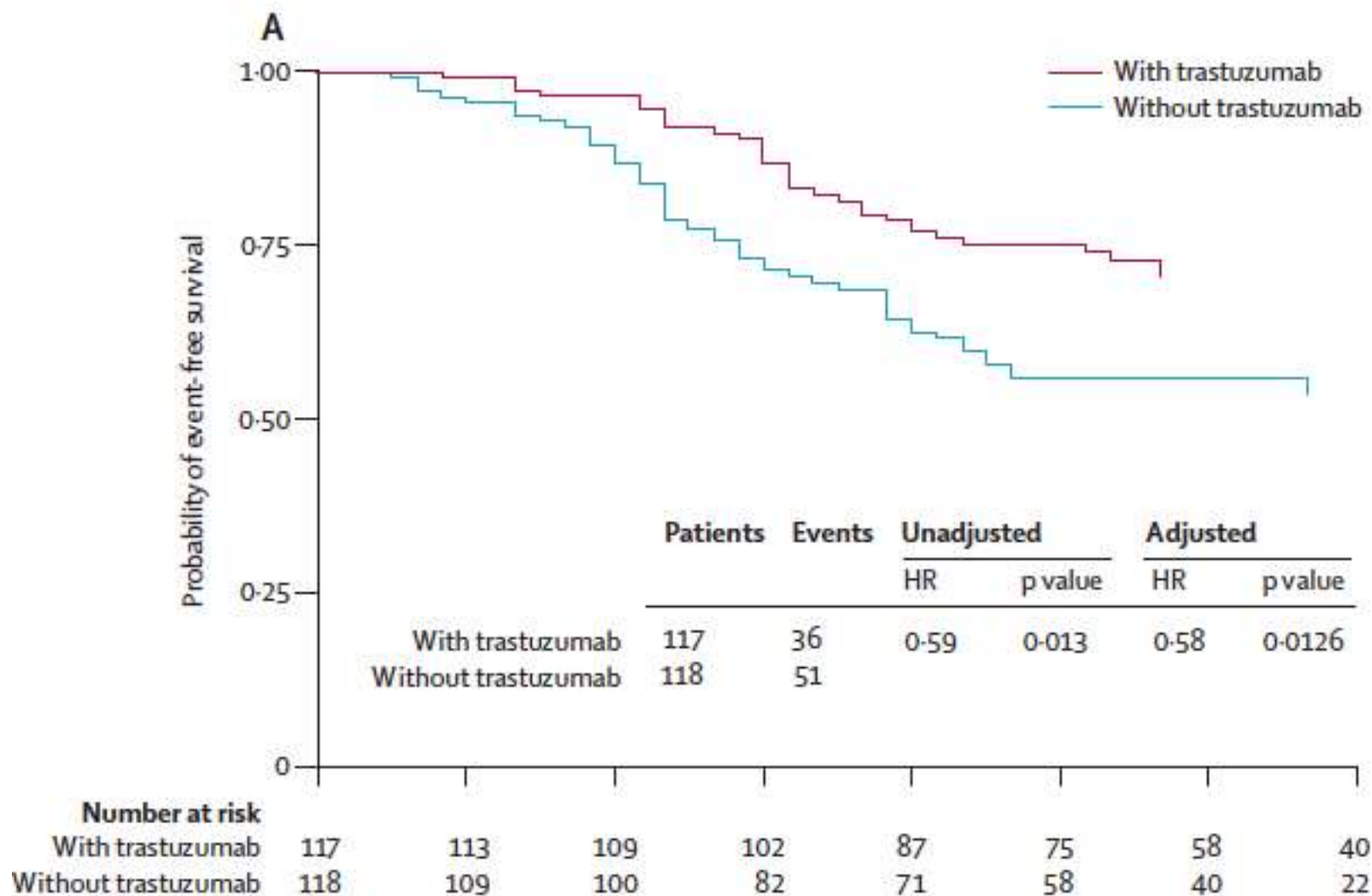
Buzdar A et al., Clin Cancer Res, 13:228-233. 2007

# HER 2 - pos

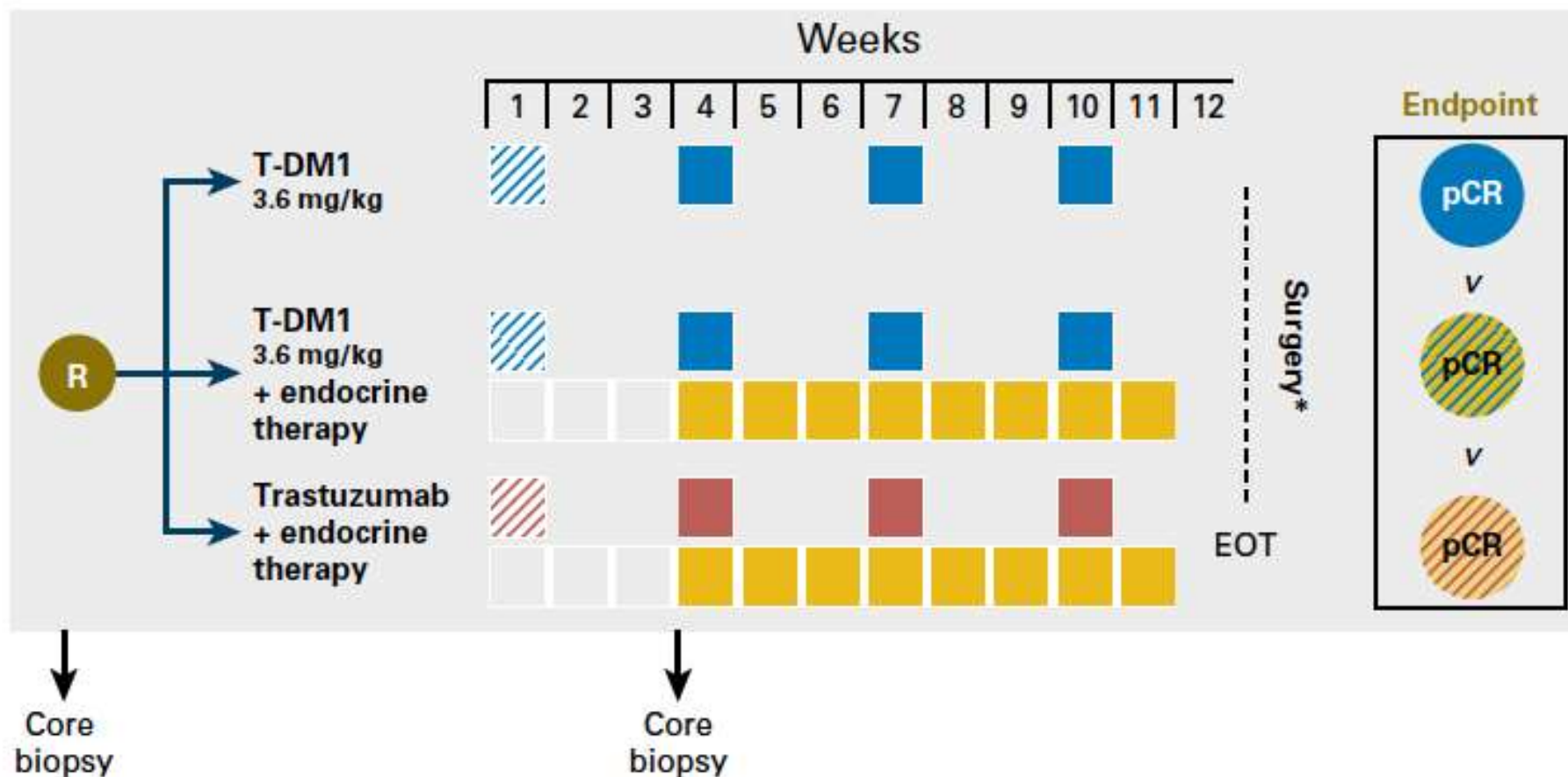
## NOAH Trial: Study Design



Gianni L, et al. *Lancet*. 2010;375:377-384.<sup>[1]</sup>



## De-escalation strategies in Her 2 positive after pCR ADAPT trial



***In 47 occurrences of pCR (40%), patients and physicians opted for no additional chemotherapy; survival follow-up in these patients will be documented and reported***

## But what about pCR in the different subtypes?

Could we omit adjuvant therapy in some circumstances?

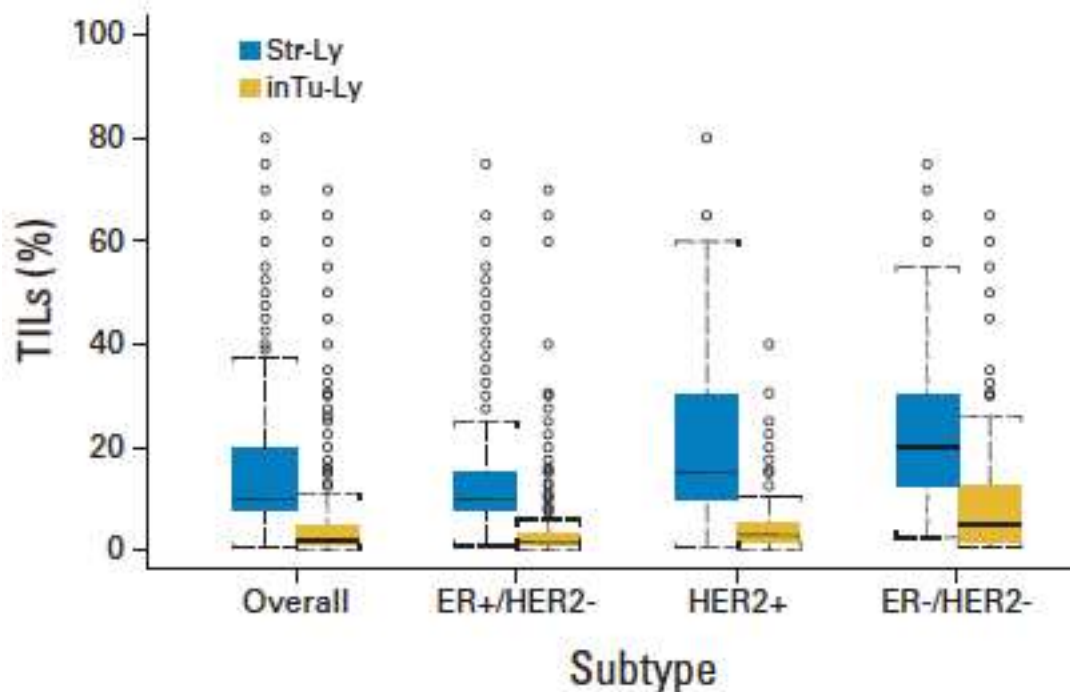
- We need randomized trials to evaluate a de-escalation in some subtypes?
- No data from randomized trial in patient with pCR after NACT
- Could we select the patients with pCR with minimal residual disease ?

TILs, CTC, ctDNA ?



**Could we select the patients with pCR to optimize  
adjuvant therapy?**

## TILs – different expression in the different subtypes



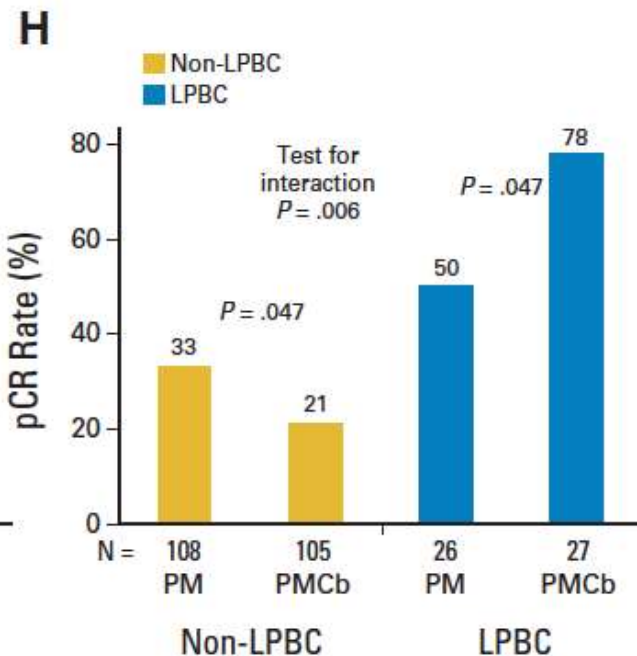
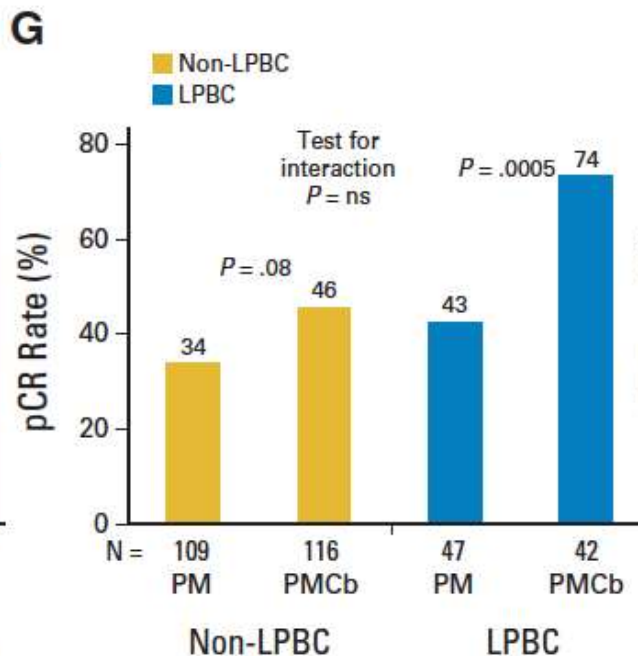
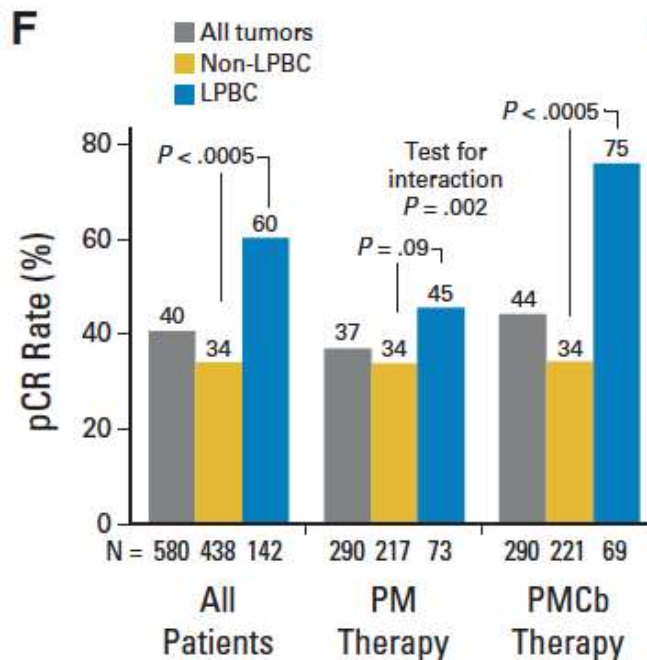
n	2,009	2,009	1,079	1,079	297	297	256	256
Min	0.5	0	1	0	0.5	0	2.5	0.5
Q1	7.5	1	7.5	1	10	1.5	12.5	1.5
Q2	10	2	10	1.5	15	3	20	5
Q3	20	5	15	3.5	30	5.5	30	12.5
Max	80	70	75	70	80	40	75	65

Loi S J Clin Oncol 31:860-867. © 2013

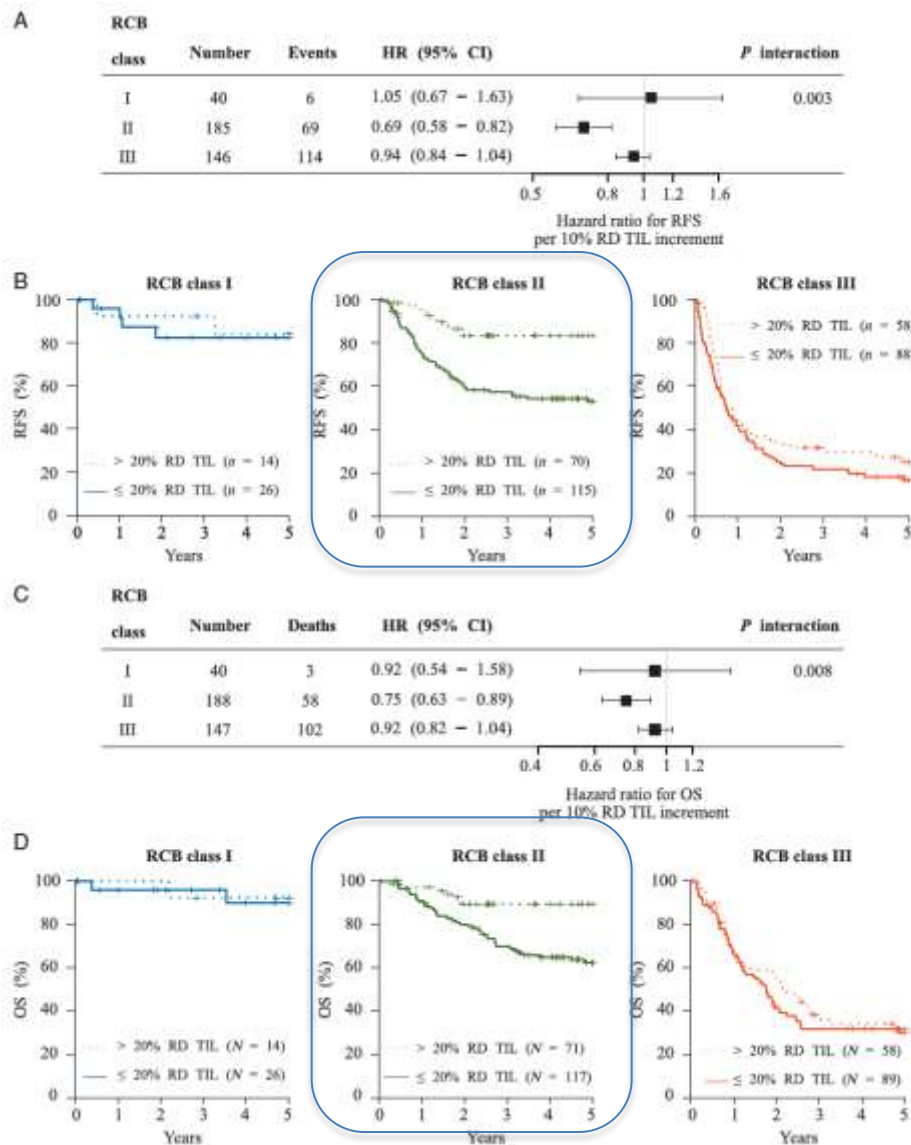
Outcome	Each 10% increment in sTILs corresponded to an HR
iDFS	0.87 (95% CI, 0.83 to 0.91)
D-DFS	0.83 (95% CI, 0.79 to 0.88)
OS	0.84 (95% CI, 0.79 to 0.89)

Outcome NO pt sTILs $\geq$ 30%	HR
3y iDFS	92% (95% CI, 89% to 98%)
D-DFS	97% (95% CI, 95% to 99%)
OS	99% (95% CI, 97% to 100%)

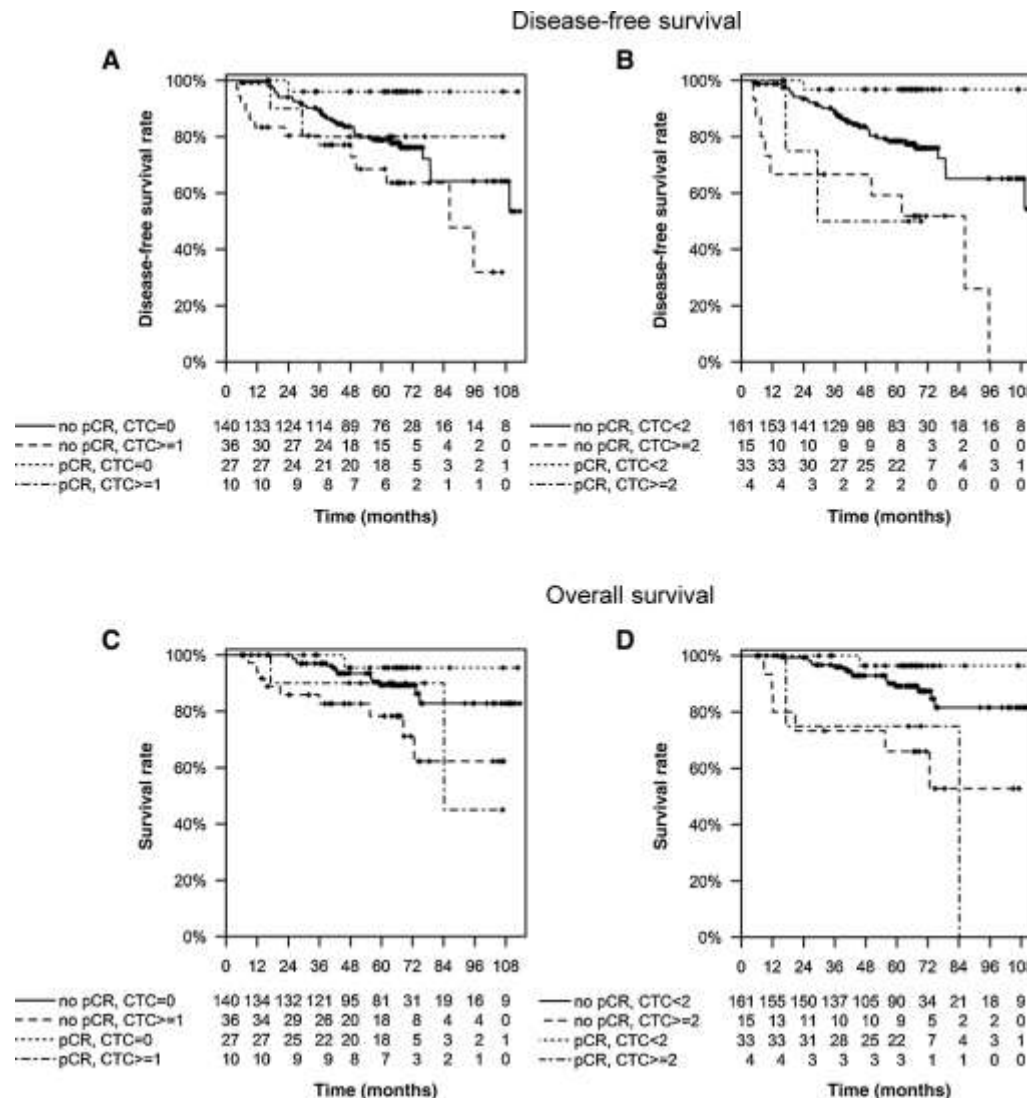
## LPBC – stromal TILs - was an independent predictor of pCR (OR, 2.66; 95% CI, 1.76 to 4.02; P .001)



Denkert C, *J Clin Oncol* 33:983-991. © 2014

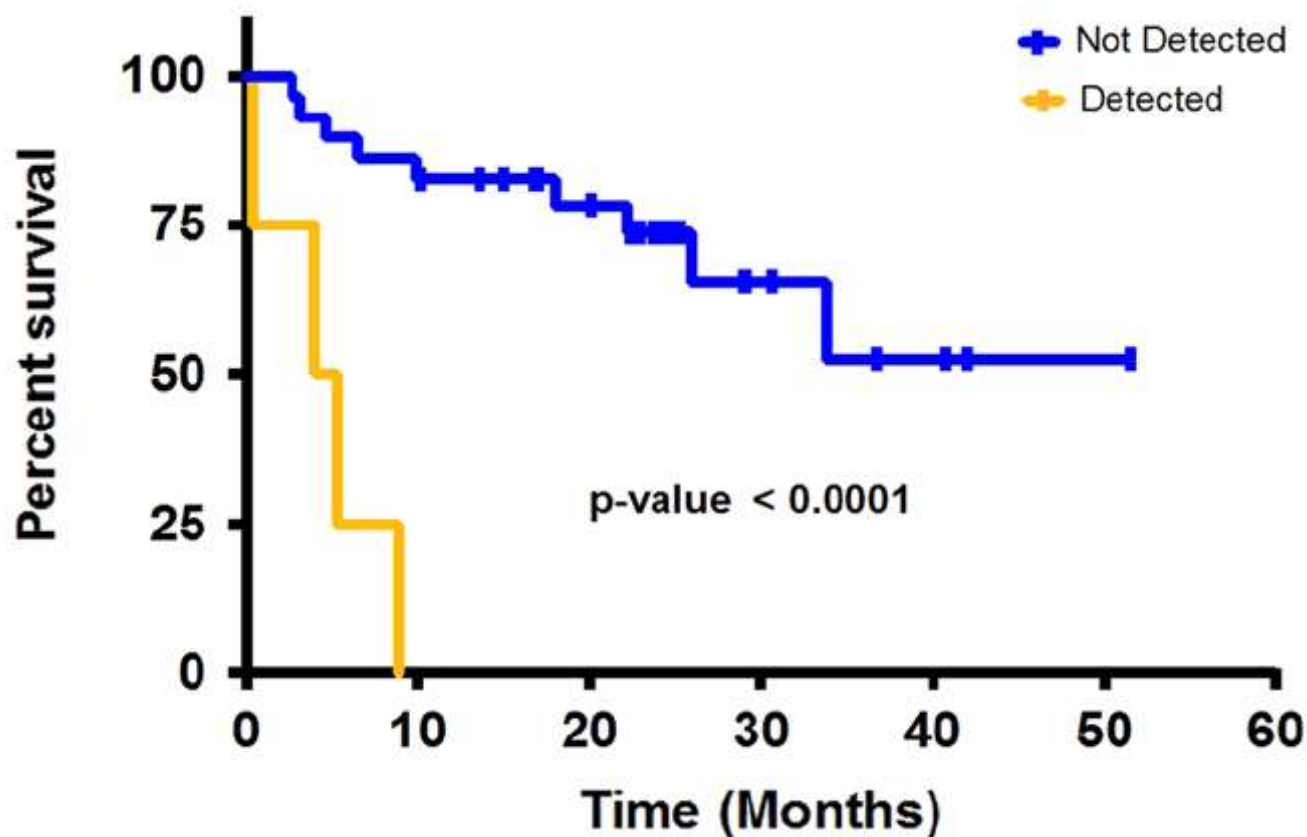


# Prognostic Impact of Circulating Tumor Cells for Breast Cancer Patients Treated in the Neoadjuvant "Geparquattro" Trial



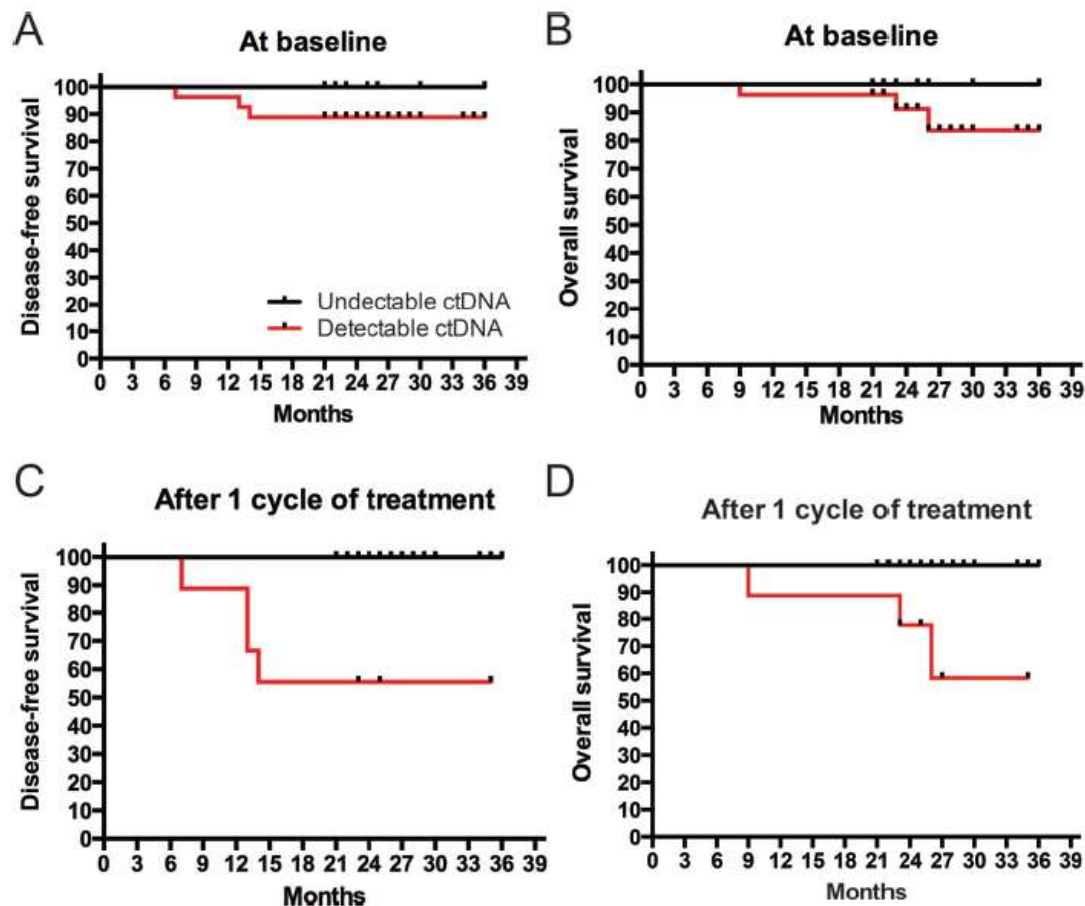
## Next-generation sequencing of circulating tumor DNA to predict recurrence in triple-negative breast cancer patients with residual disease after neoadjuvant chemotherapy

BRE09-146 DFS Stratified by Presence of Tumor Mutation in Plasma



Yu-Hsiang Chen *npj Breast Cancer* (2017) 3:24

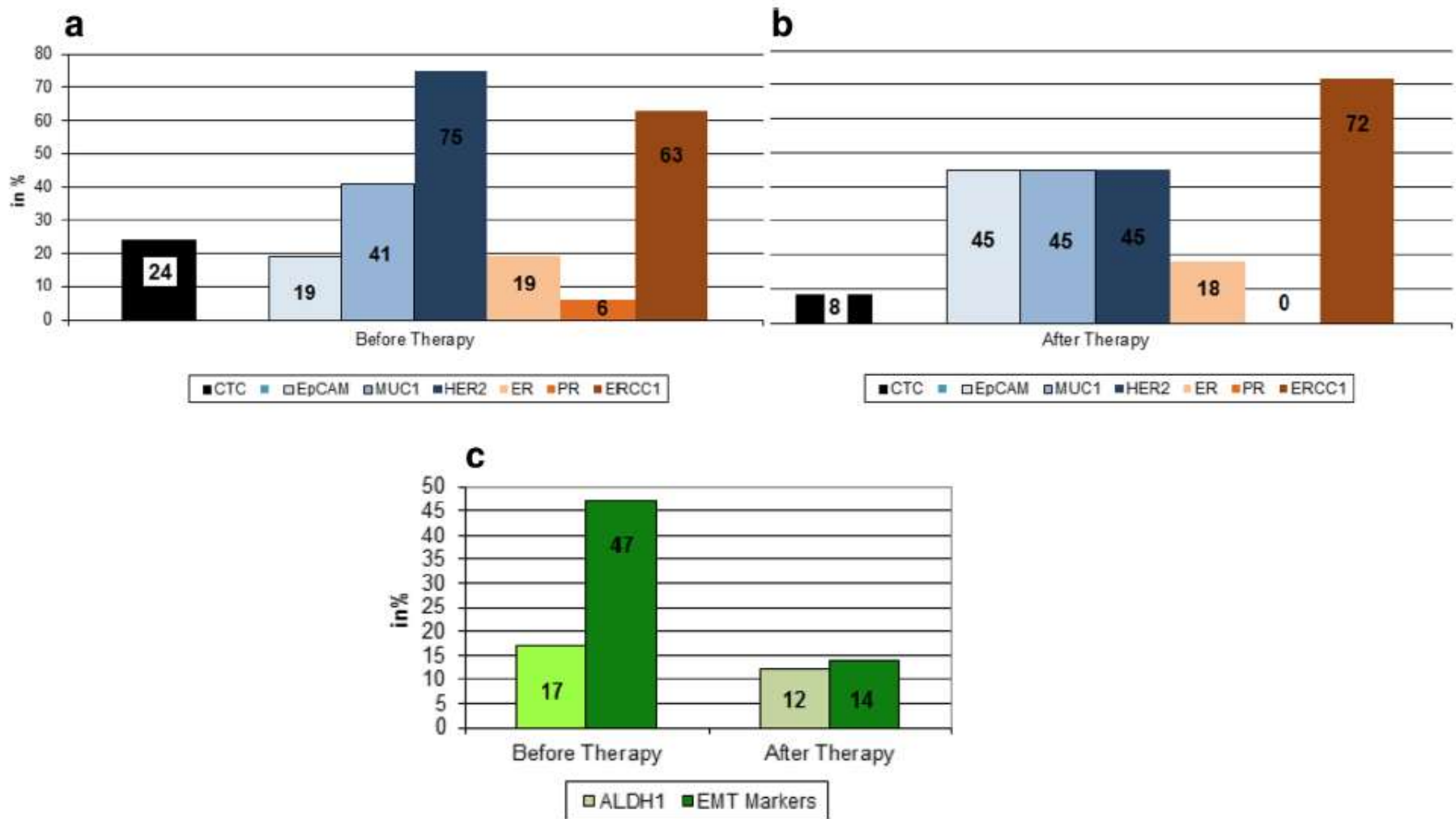
# Patient-Specific Circulating Tumor DNA Detection during Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer



*No significant association between ctDNA levels (at any of the 4 tested time points) and pCR was observed.*

Riva F, *Clinical Chemistry* 63:3 691–699 (2017)

## Does primary neoadjuvant systemic therapy eradicate minimal residual disease? Analysis of disseminated and circulating tumor cells before and after therapy

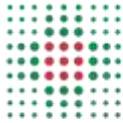


Kasimir-Bauer et al. *Breast Cancer Research* (2016) 18:20

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